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SOME STUDIES ON SUGAR IN INFANT FEEDING*

LANGLEY PORTER, M.D.
SAN FRANCISCO
AND
CHARLES HUNTER DUNN, M.D.
BOSTON

Some years ago Finkelstein[1] caught the attention of the world by formulating a new conception of the underlying causes of what were then considered diseases of gastro-intestinal origin. He described them as purely nutritional disturbances, divorced them from any relationship with the bacterial invaders of the intestine, and laid the blame of their genesis on an element of diet that had heretofore been considered innocuous, namely, the sugar. Especially did he attribute that serious, acute form of infantile disease accompanied by stupor, mellituria, and fever to the sugars. The last two symptoms were, he taught, directly and proportionately due to its presence in the food. Later, he implicated the mineral salts of cows' milk, still later prepared his celebrated "Eiweissmilch" and offered it as a remedial food for sugar intoxications, apparently overlooking the fact that as this mixture contained 1.5 per cent. of the deadly lactose its use in practice contradicted his theory. Lactose was especially the sugar he feared, so much so that he stated that even minute doses of milk containing its natural carbohydrate were damaging. Babies were injured with lactose, dextrose, lactose salt mixtures, and dextrose alkali or lactose alkali mixtures, given in isotonic, hypertonic, or hypotonic proportions. The injury was considered always to express itself in mellituria and fever, and F. M. Schapps, Leopold and Von Reuss were one in thinking with Finkelstein that lactose was "exquisitely pyrogenic." This point was emphasized by the findings of Finkelstein and Meyer that 3 gm. of sodium chlorid in 100 c.c. of water given by mouth could produce fever in many healthy infants, while if nutritional disorders were present 1 gm. sufficed to produce pyrexia.

In the next few years the men of this school decided that sugar damage was not alone a simple sugar injury, but made itself felt as the result of the previous or coincident action of salts in improper

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proportions in the food, the presence of the chlorin ion combination with sodium being especially blamed. About four years ago the idea that fermentation of sugar in the intestine played some rôle in these disorders began to be emphasized in Finkelstein's writings, and Finkelstein and Meyer laid greater stress on the fermentation of lactose in the intestine and less on the toxicity of sugar acting parenterally. They even admitted that human milk, which of course is high in lactose, may be the optimum food for certain of the cases that occurred under their classification of intoxication, apparently thus abandoning the view that milk sugar is a fatal poison in such disorders. This inference from the writings of Finkelstein is confirmed by his pupil Schultz, whose experiments did not bear out the pyrogenic or intoxicating action of the sugars. The latest position of Finkelstein's school seems to be that fermenting lactose injures the permeability of the intestinal wall, permits the absorption of salts in abnormal kind or quantity, and that these salts, either alone or in combination with the sugar, produce the poisoning which is evidenced by the glycosuria.

As to fever, there was some reason to believe that when it occurs it is the result of tissue damage such as is often seen following injections of sterile water or salt solution when they break up the erythrocytes, analogous to the fever not at all infrequently seen in childhood that follows extensive bruising or the production of hematomata.

The most convincing work among the group of men that oppose the Finkelstein-Langstein view was done by Allen working in Rosenau's laboratory. In a long series of experiments with animals in the nursling stage the effects of sugars were tested when given both by mouth and subcutaneously. Experimental animals were used and the experiments ingeniously devised to meet all objections. The animals were given large doses and small doses, some were given repeated injections and some single large doses. Those animals which received their sugars by mouth, especially lactose, showed as effects vomiting and diarrhea, which undoubtedly were due to the fermentation of the sugars in the intestine. In no one of the animals was there any sign or symptom of an intoxicating action of sugar, nor was Allen able to produce any symptoms at all approaching the clinical picture of the sugar intoxications as outlined by the Germans. On the contrary, in spite of glycosuria, which occurred in all experimental animals, he was able to see that subcutaneous injections of glucose were very definitely beneficial to his kittens and puppies, especially to one group that was weaned early and doing very badly. This seems a more rational finding than the view that implicates sugar as a poison to metabolism, as every one has seen the apparent benefit of glucose injections in the case of very sick babies.

The study of the literature would make it seem that the origin of the idea of sugar damage went back to Grosz, and was later elaborated by Langstein and Steinitz in a paper, "Lactase und Zucker Ausscheidung," published in 1906, which seems to have turned Finkelstein's interest toward the sugars as agents of possible damage in infantile nutritional disturbances. These authors in fourteen cases of severe gastro-intestinal disorders proved to their own satisfaction that a part at least of the sugar excreted into the urine was lactose. In five cases they found a second sugar which they believed to be galactose. They conclude that there can be no doubt that infants with severe gastro-intestinal disease excrete milk sugar, and its split-off product, galactose, in the urine, and that this excretion is independent of the excretion of lactase in the stool. They further say that in severe cases of gastro-intestinal disease only part of the milk sugar is split by lactase into dextrose and galactose. These are then burned in the organism or the galactose is excreted if the oxidizing power of the tissues has suffered. The second portion is absorbed unsplit and excreted as lactose in the urine. They admit that the largest proportion may be split by fermentation in the intestine and may be lost to the organism.

The views of Kendall are that lactose, far from being an injurious food, is of essential importance in so maintaining the flora of the intestine that the fermentative processes will always be slightly dominant, and will prevent the putrefactive action on protein which produces soluble toxin of undoubted damage to the general metabolism. The work of Allen and the paper of Kendall are both worthy of very close study by any one who is interested in the subject. Raphael showed that many patients assimilate large doses of sugar better than small ones. Schlessinger says that the appearance of the traces of sugar in the urine are no indication that the sugar tolerance of the body has been passed. Naunyn says that small traces of sugar may be ignored in animals who may show a slight glycosuria, with small doses and none with large. Platenze says sugar is often to be found in urine of babies who show no sign of intoxication and who seem perfectly well.

The dosage usually given for pure dextrose as one that will exceed the sugar tolerance is between 100 and 250 gm. for the adult, but many individuals can assimilate more. After the subcutaneous injection of 100 gm. of glucose, glycosuria may last as long as eight hours. The single dose maximum seems to be from 2 to 4 gm. per kilo, by mouth, 10 gm. per kilo per day, and subcutaneously 1 to 1.5 gm. per kilo per dose.

The presence of traces or of even considerable amounts of reducing bodies in the urine does not mean that sugar is present. Schultz says that a reduction test which will exclusively demonstrate the presence

of sugar is not known, and further, reducing substances such as uric acid, creatinin, albumen, coloring matter, acetone, glycuronic acid, all or any may be present. Fluckiger reports the presence in normal adult urines of non-fermentable reducing bodies which produce osazones of a value equal to 1/1500 to 1/2500 gm. of grape sugar in the twenty-four hours. Salkowski put it at 0.4 gm., Monk at 0.3 gm., and other observers at variable points. Creatinin has especially been dealt with by Sedgwick, Steinitz, Fluckiger, Amberg and Morris, so that it is clear that in infants' urines there may be considerable reducing power due to bodies other than carbohydrates, a fact well substantiated for the normal urine of adults.

This fact, together with the report by the Finkelstein school of the frequent presence of sugars in the urines of infants suffering with a less severe nutritional disturbance, made it seem desirable to test the urine of a group of infants in the Boston Infants' Hospital, who were suffering from what would be known in Europe as "balance disturbance," but which in the nomenclature of the Boston school is called "chronic indigestion." There were eighteen of these babies investigated; none of them were of the premature type such as Aschenheim found to have intestines more permeable to sugar than those of older nurslings. The first tests were all made while the children were receiving what was considered a normal amount of sugar advisable for their individual peculiarities. Later, attempts were made on a number of the cases to find the limit of physiologic tolerance for the sugars. The reagent used in the determinations was one recommended by Folin as the most sensitive to reducing bodies. It was made in two solutions, of which 3.5 c.c. of each were mixed at the time of using and from 1 to 3 c.c. of the urine added after boiling the mixture. The mixture was then centrifuged. Solution 1 contained copper sulphate 10 gm., glycerin 150 c.c., and water to make 500 c.c. Solution 2 contained 500 c.c. of a 50 per cent. solution of potassium carbonate. This reagent has shown definite amounts of reducing bodies in every adult urine tested with it. This is not true of infants' urines. Twelve per cent. showed no reduction whatever, and of the remainder, 50 per cent. gave no reduction on repetition of the test after saturation with picric acid and shaking through ten minutes to remove the creatinin which is present in appreciable quantities in nearly all infants' urines, and which reduces nearly all the copper reagents especially the more delicate. In none of the urines was it possible to measure the reduction quantitatively by Benedict's solution.

The fact having been determined that there was no measurable sugar in any of the urines tested, attempts were made to pass the sugar tolerance limit of 2 to 4 gm. per kilogram of body weight without the production of a measurable glycosuria. Such attempts

have been made before and have always failed to cause a glycosuria except in those cases of deep intoxication such as were studied by Finkelstein and his pupils.

A summary of the work done in this investigation is as follows: Patients observed, 18; samples of urines tested, 105; number of tests made, 235; signs double + and triple + are used as follows: + indicates on the addition of the urine to the heated reagent a few grains of copper oxid; ++ indicates that on centrifuging definite layer of copper oxid forms in the bottom of the tube; +++ that there is a visible reduction in the tube before centrifuging. Sixteen of the eighteen patients showed reducing bodies in some tests before the treatment with picric acid. Eight showed a loss of reducing power after shaking with picric acid. Three of the patients (+++) showed appreciable amounts of reduction constantly in all samples of urine after the picric acid treatment. One of these had an eczema corresponding in type to the exudative diathesis of the Czerny school, but in spite of the fact that this patient received as much as 120 gm. of lactose, 15 per cent. of his intake per day while he was receiving 4 per cent. of fat at the same time, there was never enough sugar in the urine to be assured by any of the usual quantitative methods and coincidently the skin condition improved steadily under local treatment. The other two patients of this group were suffering from rather extreme malnutrition. Of the 105 samples of urine, 58 showed reducing powers to our solution before shaking with picric acid. Of these 58, 27 lost their reducing power after such treatment. Of the eighteen patients, excepting the three referred to above, none showed reducing bodies every day, and in no instance did there seem to be any relation between the amounts of sugar ingested and the presence of these bodies as they were found in the urine with minimum intake, and were frequently absent following the highest ingestion.

The clinical results in these cases in which an effort was made to surpass the supposed limits of sugar tolerance were very interesting. Not knowing how severe the symptoms of intolerance might prove to be, we did not wish to give large doses of sugar suddenly, but adopted the method of a gradual increase in the amount of sugar given. The percentage of sugar in the food was increased at the rate of 0.5 per cent. a day until symptoms of intolerance developed. Lactose only was used in nine cases, dextrimaltose only in 1 case, and the tolerance for both lactose and dextrimaltose was tested in six cases.

None of the cases tested were of the severest type of malnutrition. One or two of the patients were babies having no gastro-intestinal disturbance. One presented a case of congenital obliteration of the bile ducts. The majority were babies who had presented difficult

feeding cases in the Out-Patient Clinic, and had been sent in to the hospital to be straightened out. None showed any marked intolerance for any of the food elements. The majority were comparatively mild cases of fat intolerance, showing indigestion and excessive fat in the stools when the fat was increased. No case known to have a marked intolerance of carbohydrate was tried.

Symptoms of intolerance developed eventually in twelve of the sixteen cases. Three patients were taken home, and one patient died, before the experiment was completed.

TABLE 1.—MAXIMUM SUGAR TAKEN WITHOUT SYMPTOMS

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1	Lactose, 9.5	91	9	2.25
2	Lactose, 7	83	20	3.00
3	Lactose, 14.5	169	31	4.75
4	Lactose, 14	119	40	4.00
5	Lactose, 11.5	134	28	4.00
6	Lactose, 15.5	144	32	4.40
7	Lactose, 8.5	79	18	3.00
7	Maltose, 9.5	91	20	3.00
8	Lactose, 15.5	168	27	4.50
9	Lactose, 5	53	10	2.00
9	Maltose, 12.5	158	27	4.50
10	Lactose, 7.5	67	24	2.00
11	Lactose, 8.5	100	20	3.00
11	Maltose, 8.5	100	20	3.00
12	Lactose, 12	160	17	3.00
13	Maltose, 11.5	119	33	3.10
14	Lactose, 10.5	140	30	3.00
14	Maltose, 18.5	170	54	5.40
15	Lactose, 11.5	150	18	3.00
15	Maltose, 17.5	225	27	4.50
16	Lactose, 13	146	22	3.10
16	Maltose, 18	182	30	4.00

The symptoms of intolerance were very constant. The first symptom, showing the coming on of intolerance, was marked irritation of the skin of the buttocks, in spite of the most careful nursing. The symptoms which soon followed were loose green movements, usually about five or six daily, distention of the abdomen with gas, eructations of gas, and vomiting. Loss of weight was slight; on the development of distinct signs of intolerance, the sugar was at once cut down. In no case were seen any toxic symptoms, or any signs of sugar intoxication, or any fever, except that one case developed fever at about the

time of the other signs of sugar intolerance, but at the same time this baby had an acute otitis media. The symptoms of sugar intolerance, therefore, judging from this series of cases, are in no way suggestive of intoxication, but are suggestive only of a fermental process localized within the intestinal canal.

The amount of carbohydrate taken without intolerance was surprising. The quantities of sugar given to the several cases are shown in the tables. Table 1 shows the maximum quantities of sugar taken

TABLE 2.—AMOUNT OF SUGAR ON WHICH SYMPTOMS OF INTOLERANCE DEVELOPED

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1 *	.....	...	...	...
2 †	.....	...	...	...
3	Lactose, 15	141	26	4.0
4	Lactose, 14.5	113	40	4.0
5	Lactose, 12	144	30	4.25
6	Lactose, 16	146	32	4.40
7	Lactose, 9	76	17	3.00
7	Maltose, 10	105	32	3.20
8 †	.....	...	...	...
9	Lactose, 6	53	10	2.00
9	Maltose, 13	150	26	4.60
10	Lactose, 8	72	26	2.00
11	Lactose, 9	105	20	3.00
11	Maltose, 9	105	20	3.00
12	Lactose, 12.5	172	18	3.00
13 †	.....	...	...	...
14	Lactose, 11	145	30	3.00
14	Maltose, 19	170	55	5.40
15	Lactose, 12	152	18	3.00
15	Maltose, 18	227	19	4.50
16	Lactose, 13.5	148	22	3.10
16	Maltose, 18.5	186	31	4.00

* Patient died before intolerance developed.
† Patient discharged before intolerance developed.

without intolerance. These quantities were in general far above the supposed limit of 10 gm. daily per kilogram of body weight. The percentage of sugar taken without intolerance varied from 5 to 18.5 per cent., the grams in twenty-four hours varied from 53 to 225, the grams daily per kilogram of body weight varied from 9 to 54, and the grams of sugar at a feeding per kilogram of body weight varied from 2 to 5.40. The quantities on which intolerance eventually developed were slightly higher, and are shown in Table 2. Only one baby in

TABLE 3.—Periods of Increased Sugar, Quantity of Sugar Taken, and Gain or Loss in Body Weight

Case	Food	Period of Increased Sugar (Days)	Percent. of Sugar in Food at Beginning of Period	Percent. of Sugar in Food at End of Period	Sugar in 24 Hours per kg. of Body Weight at Beginning of Period gm.	Sugar in 24 Hours per kg. of Body Weight at End of Period gm.	Gain or Loss in Body Weight During Period gm.	Average Daily Gain or Loss in Body Weight During Period gm.
1	Lactose	8	9.5	9.5	9	9	— 500	— 63
2	Lactose	13	7.0	7.0	20	20	+ 290	+ 22
3	Lactose	20	7.0	15.0	16	31	+ 780	+ 36
4	Lactose	18	7.0	14.5	22	40	+ 120	+ 7
5	Lactose	18	6.5	12.0	18	28	+ 330	+ 13
6	Lactose	20	6.5	16.0	14	32	+ 670	+ 33
7	Lactose	8	5.5	9.0	13	18	+ 220	+ 27
7	Maltose	10	6.0	10.0	14	20	+ 260	+ 26
8	Lactose	19	6.5	15.5	12	27	+ 1,000	+ 52
9	Maltose	16	6.0	13.0	14	27	+ 500	+ 31
10	Lactose	4	6.5	8.0	21	26	+ 120	+ 30
11	Lactose	7	7.0	9.0	16	20	+ 30	+ 4
11	Maltose	7	7.0	9.0	16	20	+ 90	+ 13
12	Lactose	13	6.5	12.5	9	18	+ 210	+ 16
13	Lactose	20	6.5	16.5	11	33	+ 1,000	+ 50
14	Lactose	7	7.0	10.5	20	30	+ 200	+ 27
14	Maltose	22	7.0	18.5	20	55	+ 680	+ 30
15	Lactose	10	6.5	11.5	9	18	+ 220	+ 22
15	Maltose	22	6.5	17.5	9	28	+ 790	+ 36
16	Lactose	13	6.5	13.0	14	28	+ 250	+ 19
16	Maltose	22	6.5	18.0	14	36	+ 580	+ 26

the series showed inability to take more than 7 per cent. of sugar, or more than 10 gm. per kilogram of body weight in twenty-four hours.

In the six cases in which the comparative tolerance for maltose and lactose was tried, it was found to be about the same in two cases, but distinctly higher for maltose than for lactose in the other four cases. In no case was there the slightest evidence of any relation between the amount of sugar given and the presence of a positive sugar test in the urine. The sugar was just as likely to be absent as present in cases taking a maximum of sugar, or in cases showing symptoms of intolerance. The three cases showing the constant presence of sugar, showed the same reaction irrespective of the amount of sugar given. The other cases show positive and negative urinary tests at all stages. The last three cases, numbered 14, 15 and 16, showed sugar more often present with maltose than with lactose. Whether this is the rule requires further observation.

The effect of the increased quantity of sugar on the weight curves of the babies was most surprising, and is shown in Table 3. The majority of the cases not only gained weight, but gained weight very rapidly during the period of sugar increase. Also the gain, while less rapid after sugar intolerance developed and the sugar was cut down, was in all cases maintained. In some instances the gain was really enormous. Patients 8 and 13, both on lactose, gained 1,000 gm. in twenty days. Only one case, which afterward proved to be tuberculous, failed to gain. Excluding this case, the average daily gain for the whole series during the sugar period was 26 gm.

It seems to us that the idea of sugar injuries and sugar intoxication has possibly kept us from the use of large amounts of soluble carbohydrate in certain cases, particularly those unable to take a quantity of fat sufficient to meet their nutritive requirements. That many such babies have intolerance of sugar is indoubtedly true. But the danger of pushing the sugar to the limit of tolerance we believe to have been exaggerated. The signs of sugar indigestion are distinct and easily recognized, and do not appear to be in any way serious. In many cases great benefit appears to be obtainable by greatly increasing the carbohydrate content of the food, and therefore this proceeding may prove a valuable addition to our stock of resources in dealing with difficult feeding cases.

240 Stockton Street, San Francisco—178 Marlboro Street, Boston.

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PYLORIC HYPERTROPHY IN NEW-BORN INFANTS

F. L. WACHENHEIM, M.D.
Attending Pediatrist, Sydenham Hospital
NEW YORK

During the last ten or fifteen years, in which hypertrophic pyloric stenosis and pylorospasm in infants have been the objects of absorbing interest, the prevailing tendency has been to draw well-defined clinical pictures of these two affections, and to distinguish them sharply from normal conditions, as well as from each other. With regard to the latter distinction, the chief object has been to define the operative indication; we have now come to understand that this end is not always attainable, and that difficult borderline cases form a large proportion of the total. As a matter of fact, the absence of any sharp dividing line was more than suspected ten years ago by Ibrahim,[1] and has recently been reaffirmed by Holt.[2] Careful study of the best contributions to the subject conveys the impression that this attitude of uncertainty pervades most of the literature; only the surgeons, possessed of a more limited view, seem to maintain rather positive opinions, where the pediatrists are vexed with doubts.

With the aid of certain postmortem material that has recently been at my disposal, I shall endeavor to show that even the first proposition, namely, the diagnosis between pyloric hypertrophy and presumably normal conditions, is beset with difficulties, and that, as a consequence, the distinction between spasm and true organic obstruction is likely to remain, in many cases, a matter of great uncertainty unless new diagnostic methods are brought to our aid.

The following new-born infants were examined:

CASE 1 (No. 15887).—Baby S., premature, died in the third week, of atelectasis. The pylorus forms an obviously thickened mass, its walls being about 4 mm. in diameter, but the lumen appears to be fully normal. The pylorus as a whole projects into the duodenal canal very much in the manner of a cervix uteri, and as described in cases of true pyloric hypertrophy.

CASE 2 (No. 15894).—Baby S., died on the fifth day, of hemophilia of unknown origin. The same condition of the pylorus is found, the lumen of the organ measures 6 to 7 mm. in diameter.

CASE 3 (No. 16149).—Baby S., died on the fifth day of multiple hemorrhages. The pylorus presents the same thickening of the walls, and projection into the duodenum, with a lumen of 8 to 9 mm.

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* Submitted for publication June 6, 1915.

1. Ibrahim: Die angeborene Pylorusstenose im Säuglingsalter, 1905.
2. Holt: Medical Versus Surgical Treatment of Pyloric Stenosis in Infancy, Jour. Am. Med. Assn., June 17, 1914, p. 2014.

CASE 4 (No. 16148).—Baby C., died in the third week, of congenital atresia of the bile ducts. Pylorus exactly as noted in Case 3.

By way of comparison, I give two autopsies of older infants.

CASE 5 (No. 15818).—Frances K., died at 3 months of meningitis. The pylorus is little, if at all, thicker than the duodenum, and does not project into it; the pyloric wall is of about normal thickness.

CASE 6 (No. 16364).—Frank E. died in the fourth month, of an exceptionally severe purulent meningitis. There is in this case a slight thickening of the pyloric wall, but less marked than in any one of the four new-born infants.

To these I may add a previously[3] reported control case:

CASE 7.—Died in the eighth week, of gastro-enteritis. Pyloric wall is not at all thickened, measuring 2.5 mm. in diameter; the viscus does not project into the duodenum.

SUMMARY

In summarizing the above cases, I wish, in the first place, to call attention to the substantial uniformity of conditions in the first four cases, which were consecutive, not selected, and in which the pyloric findings were accidental, and not sought for. The conditions in any one of these four infants might have led to pyloric spasm, which, according to Ibrahim,[1] is a probable causative factor in the development of true organic obstruction.

In the middle period of infancy, we have plainly a different state of affairs in the normal subject. There is usually no thickening, or it is, at any rate, very slight, as in Case 6. As far as can be determined from so small a material, a retrogressive change normally takes place between the third week and the third month, in the course of which the very perceptible thickening of the pylorus gives way to a condition in which the borders of that organ are macroscopically almost undistinguishable.

The first group of cases presented no symptoms of spasm or obstruction. The latter was plainly not present, and the former does not occur, even in predisposed cases, until the third week of life. The stated findings do not, therefore, conflict with our clinical observations. The question of a postmortem contracture, long since thrashed out, is here refuted by the conditions noted in the second group; also in a few of these cases by the performance of the autopsy after rigor mortis had disappeared. As in obstructive hypertrophy, so in these cases, the total bulk of the viscus was greatly increased; in postmortem spasm the increased thickness would be compensated by an equivalent shortening of the organ.

The thickness of the pyloric wall in the normal infant of two months is 2 to 2.5 mm., in the new-born it is greater, 3 to 4 mm., in established hypertrophic stenosis fully 5 mm.; evidently the conditions in the new-

3. Wachenheim, F. L.: Am. Jour. Med. Sc., April, 1905.

born are intermediate, and it depends on circumstances whether the normal retrogressive change takes place, or the thickening increases to such a degree as to cause obstruction. Possibly the development of the latter condition is due to hyperacidity and consequent pylorospasm, leading to hypertrophy, as is believed by some authors, but this sequence is so far purely conjectural. At any rate, the average new-born infant bears within itself the latent tendency to develop pyloric hypertrophy, and it depends on factors hitherto uncontrollable whether the stated condition develops or the pyloric wall thins out in the normal course.

Owing to the small number of cases in my series it would be presumptuous to state that the pyloric thickening in the new-born is universal; its occurrence in four consecutive cases seems to show that it is present at least in the majority, but further research along these lines is imperative, and may lead to valuable results if my observation is confirmed by other investigators. Further research may also lead to an explanation why some infants never get beyond the clinical picture of pylorospasm, whereas a considerable number go on to true organic obstruction. The working out of prophylactic measures may likewise result from further studies; in this respect the present dietetic treatment of pylorospasm possibly points the way.

I wish to thank my adjunct, Dr. B. M. Wronker, for valuable assistance.

111 West Eighty-fifth Street.

STUDIES IN BRONCHIAL GLANDS*

WILLIAM W. HOWELL, M.D.
BOSTON

The impetus for this study of bronchial glands came from what seems to be the growing opinion that chronic adenitis of the bronchial glands is always tuberculous. This opinion may have arisen from the specialist in tuberculosis or from those examining sick children for possible tuberculosis, for by such is an examination of these glands usually made.

In order to determine the frequency of chronic adenitis of the bronchial glands in infancy and childhood, the reliability of the signs, and the possible pathology of the gland, I have examined, during the past year, all cases coming under my care, no matter for what reason. This series of cases came from three sources: from the Infants' Hospital, from a large school and from private practice. At the Infants' Hospital the patients were infants under 2 years, admitted for non-contagious medical diseases including nutritional disturbances. This gave over three hundred cases. The school is located in a healthy suburb of Boston and draws children from families of moderate circumstances and is not a tenement district. There are 700 in the school, but only 500 between 6 and 13 years of age are included in this series. The cases seen in private were in and about Boston, and were those usually seen in general practice confined to infants and children.

The means used to demonstrate enlarged glands were auscultation and percussion, the Roentgen ray being employed to confirm physical signs. By auscultation I mean determination of the sign described by D'Espine as the point on the vertebral column at which whispered voice changes from a vesicular to a bronchial character, and was given by him as taking place at the seventh cervical. In infancy it is impossible to get whispered voice, but the character of the expiration is as satisfactory, and is best heard after crying. In very few cases have I found the change as high as the seventh cervical, but commonly at the first or second dorsal, and frequently as low as the third without cause. The average height increases with age. I found no case at the seventh cervical in infancy, the average being between the second and third dorsal; at 6 years 40 per cent. had changed at the second dorsal; at 12 years 85 per cent. had changed at the second dorsal,

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* From the Infants' Hospital, Boston.

and several cases at the seventh cervical. The sign differs in degree or rather in intensity of the bronchial character, depending on the amount of gland involvement, their size and position. Just as in lung examination it is not the harshness of the breathing but its character that counts, so in the D'Espine sign it is the point where the breathing changes from vesicular to bronchial and may be loud or distant. Hence from the foregoing I have accepted as a positive D'Espine a change in character of whispered voice or expiration at or below the third dorsal.

Percussion for glands has been very difficult, and to map out with any degree of certainty the area of dulness into cone shaped and circular areas, as described by some writers, I have found difficult. Dulness to the left of the sternum and spine is masked by the heart and great vessels. Dulness in the second interspace to the right of the sternum, and dulness to the right of the vertebral column at the level of the spine of the scapula is definite and significant and seems to agree pretty well with the intensity of the D'Espine.

The Roentgen ray was used as routine only in the hospital cases. The physical examination was made and recorded, then a roentgenogram was taken to check up the physical findings. In no case with positive signs did the roentgenogram fail to show a shadow. Enough of the cases have come to postmortem to prove the reliability of the signs and the Roentgen ray.

The bronchial glands, speaking of the various groups as if of one group, may be inflamed just as any other glands may be, and may be acute or chronic or apparently chronic from constantly draining a diseased area. There seems to be a choice of glands involved depending on the source of the infection; the glands along the trachea drain the upper regions, the hilus or tracheobronchial glands drain the lung, both sets giving positive D'Espine, the hilus glands more commonly giving dulness.

Acute adenitis of the bronchial group need give little concern, for the signs disappear rapidly after the parent disease subsides. The importance of adenitis of this group seems to me to lie with the chronic ones, or those which appear to be chronic. As I said before, there is an impression that chronic adenitis of the bronchial glands means tuberculosis. If we bear in mind that tuberculosis of infancy and childhood is primarily a chronic inflammation of the glands adjacent to the portal of entry, and that the portal of entry is most often in the lungs, then the importance of chronic hypertrophy of the bronchial glands becomes apparent. The cases entering the Infants' Hospital since July, 1914, for conditions other than acute infectious diseases, and without history of recent acute infectious disease of the air pas-

sages, showing positive D'Espine and interscapular dulness with or without lung signs, have proved to be tuberculous. I shall mention a few cases in illustration.

CASE 1.—Girl baby, 15 months old, admitted for anemia following improper diet. Examination showed dulness at the right apex, distant bronchial breathing and fine râles; right interscapular dulness, positive D'Espine, Pirquet positive.

CASE 2.—One month premature girl admitted Feb. 25, 1915, for regulation of feeding and observation to find the cause for febrile attacks recurring at intervals of three weeks. Examination showed signs at right apex, interscapular dulness and positive D'Espine. Pirquet negative February 28, positive March 25.

CASE 3.—A seven months baby seen in private with the story that it could not take the bottle; had done well for four months on the breast when breast milk gave out. It seemed willing to try the bottle, but after sucking a few times gagged and spit out the milk. Adenoids had been removed without relief. Physical examination showed dulness, bronchial breathing, fine râles at the right apex, right interscapular dulness, positive D'Espine. Stomach tube passed with difficulty. Father tuberculous.

With what certainty chronic bronchial adenitis may mean tuberculosis in infancy some cases I had seen in private practice led me to believe that it might be otherwise with older children. I have watched children for months with positive D'Espine, troublesome, dry, brassy cough to have all signs disappear after removal of adenoids. Hence, to determine the frequency of positive signs and the possibility of other sources of infection I made the second part of my series of examinations, that is, in presumably well schoolchildren. This was unsatisfactory in some respects for I was not permitted to make Pirquet tests or roentgenograms and so the cases must go without these checks. All the cases were examined in the fall of 1914, and all positive cases were reexamined during the past three weeks, or at least three months after. Out of a total of 505 children examined in the school there were 112 with positive D'Espine at or below the third dorsal. Of the positive cases 96 were at the ages of 6, 7 and 8 years from a total of 297 cases at these ages. The remaining 16 positive cases were at the ages of 9, 10, 11 and 12 years. For some reason positive D'Espine was very much more frequent in the younger half, 36 per cent. as against 8 per cent. The most common defects at the younger age were carious teeth, adenoids and tonsils and if such cases had chains of enlarged glands down the neck, showed positive D'Espine.

Most of the younger children were in good condition, might have a cough but showed no malnutrition or anemia. Some of them were undernourished and anemic, and beside a positive D'Espine showed interscapular dulness or a slightly dull apex.

The older groups, sixteen in all, gave a different picture. Ten undernourished, anemic children with interscapular dulness and dul-

ness at one apex; three no dulness but anemic and undernourished; three in good condition having carious teeth and glands in the neck; no case in either group with so-called active tuberculosis meaning active pulmonary signs.

After completing the examinations I went into the histories. The same family name often appeared, and after they were grouped according to the name frequently all the children of a family in the school appeared in my series. Among the younger half there were 27 with a history of definite exposure to tuberculosis and among these were found the cases with positive D'Espine, dulness and malnutrition. In the older half, in the 13 cases with D'Espine, dulness and malnutrition there was a history of exposure in every case. The other three showed merely a positive D'Espine without dulness or malnutrition, and gave no history of exposure.

In all these cases I did not separate the glands into groups but took the signs as they came, hoping to be able to draw some working conclusions from the results. For purposes of diagnosis I think it would be well to think of these glands as of those up and down the trachea, and of those at the root of the lungs. Inflammation of both of the sets will give positive D'Espine, dulness accompanying those at the root of the lungs, and not with glands down the trachea unless there is also consolidation at the apex of the lungs. The upper set becomes enlarged from draining the upper regions and gives a narrow chain which is sufficient to transmit the bronchial character of the sounds but does not give dulness. Hence I believe a positive D'Espine with interscapular dulness means thickening at the roots of the lungs, secondary to a process in the lungs which in infancy means tuberculosis, and, in older children, if accompanied by malnutrition and anemia, is probably tuberculosis.

279 Clarendon Street.

ACUTE NONEPIDEMIC INFLAMMATION OF THE SUBLINGUAL GLANDS IN CHILDREN: AN AFFECTION OF UNKNOWN ORIGIN *

HAROLD NEUHOF, M.D.
NEW YORK

That the sublingual glands may be involved in epidemics of mumps, alone or in conjunction with the other salivary glands, is well known. Whenever reports of nonepidemic inflammation of the sublingual glands are made, well-defined local or combined general and local causes are given. The group of cases I wish to report does not fall into either of these categories. They are characterized, in brief, by the rapid development of a sublingual and median submental swelling, and fever, in previously healthy children; fever soon recedes whereas the swelling under the chin progresses, the overlying skin often becomes reddened, and, about the time the appearances point to the development of an abscess, the submental lesion slowly subsides.

Most of the patients presenting this condition (in all, about a dozen cases have been seen) have come under my observation in the surgical department of the Mount Sinai Hospital Dispensary in the past six years. The significance of the earlier cases was entirely overlooked, and no special attention was given to the submental swelling that was usually considered a lymphadenitis from an undiscoverable cause. Indeed, as recently as 1912, I operated upon one of these patients under the totally erroneous impression that I was dealing with a submental abscess. The description of this case and two more recent ones that could be followed carefully will sufficiently illustrate the clinical picture.

CASE 1.—A girl, 9 years old, came under my observation in April, 1912, in the Mount Sinai Hospital Dispensary, with the history of progressively increasing median submental swelling, some sublingual pain and fever, for five days. Local treatment had not been employed. There were no previous illnesses.

Examination.—A slightly sensitive swelling beneath the sublingual mucous membrane was found, but no focus of infection in the mouth could be discovered. The large mass below the point of the chin was brawny and tender; the overlying skin appeared adherent and was deep red.

The diagnosis of a submental abscess was made. It was determined to drain this through the mouth because the supposed abscess appeared intimately connected with the floor of the mouth. At operation the very edematous mucous membrane and submucous tissues under the tongue were incised. Dressing forceps were passed through the infiltrated submental tissues in various directions; a little clear fluid escaped, but pus was not encountered. Aspiration at several points was also negative. The wound was packed.

The postoperative course was uneventful. The submental lesion appeared unaffected by the operation; it remained unchanged in size for four days and

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then slowly receded, the overlying skin gradually assuming a violaceous hue. Nine days after the operation the submental swelling was gone, the sublingual incision healed. The patient was well when seen several months later.

CASE 2.—An obese girl aged 7 was always well except for an attack of gangrenous appendicitis with diffuse peritonitis, for which I operated in August, 1913. In February, 1914, she came under observation with a very pronounced median submental swelling of two days' duration. The child had been well since the operation; there had been no lesion of the mouth or face, no complaint of toothache. Mumps not present in any of the children in the house. Preceding the onset of the swelling there was feverishness and malaise for about twelve hours. When first noticed the submental lesion was very small and painful; it increased in size very rapidly, the mild constitutional symptoms soon disappeared. A little thickness of speech developed.

Examination.—The marked "double chin" effect of the submental swelling gives the child a very grotesque appearance. The brawny mass is the size of a small hen's egg and is capped by a red and glossy patch of skin. The latter is surrounded by a zone of tense, faintly bluish skin. The mass is not very sensitive. Adjoining it are a few small slightly tender lymph-nodes. The tongue is somewhat raised by the swelling on the floor of the mouth. The sublingual fold is very edematous; on either side the mucous membrane is domed to almost hemispherical proportions. These masses are slightly tender and doughy to the touch. As determined by combined palpation, the sublingual and submental swellings merge into one. There is no escape of saliva on pressure. Several reddish spots are seen in the sublingual mucous membrane. These appear to be the inflamed orifices of the sublingual ducts; the smallest probes could not be introduced into them.

Four days after the onset of the illness the child was seen again. The submental swelling was slightly larger and more tender; the sublingual tumefactions were smaller. Speech was normal. The general condition was excellent. Temperature, 99.8. White blood count, 10,200; 65 per cent. polymorphonuclears. The submental mass did not begin to recede until five days later. The overlying skin then began to assume a faintly violaceous color; the surrounding lymph-nodes were no longer palpable, and the sublingual swelling was gone. A small, rather firm submental mass still persisted two weeks later; it did not entirely disappear until seven weeks after the onset of the disease. The child has been well since that time.

CASE 3.—A boy 6 years old was referred for operation for submental abscess in April, 1913. With the exception of scarlet fever at the age of 3 he had always been well. There are four other young children in the family; no recent illness among them. The mother knew of no children in the house suffering from mumps. The submental swelling had been present for nine days at the time I saw the patient. The illness began with vomiting and fever (102 F), pain under the tongue, and salivation. These symptoms diminished in a few hours; a median submental swelling then appeared. The patient felt well next day except for pain beneath the jaw. The submental tumor increased in size on the third day; the temperature was 100.6. The increase in size was progressive for the following two days; no change in the succeeding two days. "A little fever" has persisted, and there has been some sweating at night.

Examination.—Excellent general condition. Temperature, 100 F. Teeth good. Examination negative except for the local findings. The median submental swelling gives the child the appearance of having a "double chin." The overlying skin is reddened, tense, and glossy. The mass is moderately sensitive to pressure; on both sides several very small lymph-nodes are felt. The sublingual mucous membrane is bulged forward by a doughy mass underneath it; several tiny red spots, presumably the inflamed orifices of the sublingual ducts, are seen in the somewhat injected mucous membrane near the median line. By combined palpation the sublingual and submental swellings are found to

comprise a single bilocular mass. No saliva can be expressed. The other salivary glands are not enlarged. No discoverable local lesion to account for the infection.

Indifferent local applications were employed. The sublingual swelling soon disappeared, but the submental tumor remained unchanged for three days after the time I first saw the patient. It then receded gradually. Fifteen days after the onset the lesion was entirely gone. The child has remained well since that time.

These cases have been selected because they could be most closely followed and were the most striking illustrations of the affection. In some of the other patients the sublingual and submental tumefaction was not so pronounced and the peculiar persistence of the latter was not so evident. External incision of a supposed submental abscess surely would have been carried out in one case[1] had the affection in question not been borne in mind. In no instance was there a history of mumps among other children in the family or elsewhere in the immediate neighborhood.

At the present time the chief practical significance of the type of sublingual gland inflammation that has been presented lies in the ease with which it may be mistaken for submental abscess or other submental lesions. A brief survey of these conditions, with the question of differential diagnosis in view, may therefore be permitted.

Judging from the literature on the subject, solitary involvement of the sublingual glands in epidemics of mumps is recognizable only when an epidemic of mumps exists or when one of the characteristic complications of mumps develops. The few descriptions of "sublingual mumps" I have been able to find do not depict the pronounced local swelling, skin redness, and peculiar persistence of the lesion so frequently seen in my series of cases. An exception, on which I wish to dwell for a moment, is the unique epidemic of sublingual gland disease described in 1913 by Hegler.[2] He observed a group of eight cases, all adult females (seven of them nurses in one hospital), in whom the disease developed about the same time. There was no coincident epidemic of ordinary mumps. The illness began with mild febrile manifestations and a rather acute onset of the sublingual and submental swelling. The latter often reached the size of a walnut and was painful; the overlying skin was tense and glossy. The resultant appearance was frequently that of a "double chin." The floor of the mouth was swollen, the sublingual fold red and edematous in several instances. The swelling often persisted for eight to fourteen days. There were no complications. Barring the fact that Hegler's patients

1. Transferred from the pediatric department of Dr. M. H. Bass, Mount Sinai Hospital Dispensary.

2. Hegler: Mumpsartige Erkrankungen der Zungenspeicheldruese (Sialoadenitis Sublingualis Acuta Epidemica), Beitr. z. Klin. d. Infectionskrank., 1913, i, 229.

were all adult females, and that the disease was of epidemic nature, it is evident that his cases closely resemble those I have described.

The nonepidemic acute inflammations of the sublingual gland (and of the other salivary glands, as well) that have been described in the literature fall into two groups—one, in which the cause is purely local, the other, in which serious constitutional disease exists. Of the former, injury to the gland, diseases of the buccal mucous membrane or in the tissues about the salivary gland, calculi or other foreign bodies in the salivary ducts or gland may be mentioned. Any of the acute infectious diseases, pyogenic infections, abdominal operations or disease, cachexias, may be complicated by sialoadenitis. Lastly, the little understood salivary gland inflammation of earliest infancy should be mentioned. These varying etiologic factors play no important part in the symptomatology of acute inflammation of the sublingual glands. The condition is usually characterized by a rather stormy course: The tongue is soon elevated by the rapidly increasing swelling of the sublingual tissues, saliva flows profusely, and speech and swallowing may be difficult. The outcome is regularly the formation of an abscess that generally ruptures into the floor of the mouth or one of the salivary ducts.

This survey of the etiology and symptoms of the ordinary nonepidemic acute inflammations of the sublingual glands suffices to show that they do not resemble the type of inflammation I have described. The same statement may be made concerning the noninflammatory (?) acute sublingual lesions termed "tumor salivis" (von Bruns) and "acute ranula." In the former there is an acute transient occlusion of the salivary ducts due to definite lesions at their mouths; in the latter the tumor is cystic and is confined to the sublingual region.

Submental adenitis and frost-bite below the chin are conditions that occasionally resemble acute nonepidemic inflammation of the sublingual glands. The source of the infection in the field drained by the involved lymph-nodes will be found almost invariably in cases of submental adenitis; in the exceptional instances only a history of a focus of infection will be obtained. Separate lymph-nodes are felt in the early stages of submental adenitis; all the evidences of an abscess are present in the later stages. Sublingual swelling is manifestly no part of the picture of submental adenitis. Sublingual swelling likewise is not associated with frost-bites so often seen in the submental region. There usually is a history of exposure to cold; the lesion primarily involves the skin and the subcutaneous swelling is evidently secondary. In my experience these frost-bites never remain stationary for more than a few days; either the skin lesion recedes under appropriate treatment or, in more severe cases, sloughing and ulceration of the skin ensue.

From these remarks it is evident that the type of inflammation of the sublingual glands I have described cannot be classified at the present time with the other lesions of the sublingual glands and ducts or of the submental region. In appearance, development, and duration the clinical picture is quite distinct. On the other hand nothing in the history or physical examination points either toward or against a uniform etiology of the affection. Bacteriologic studies will be necessary to determine if there is a specific organism similar to that producing mumps, or if various etiological factors obtain. In this connection it is of interest to note that Hegler believes that a special organism, possessing a tendency to involve the sublingual glands, is the cause of the unique epidemic he described. Although his cases appeared in adult females and those I have described were nonepidemic in children of both sexes the close parallel between the clinical pictures of the two groups, to which attention has been called, cannot be overlooked in discussing their etiology.

The fact that cases similar to those I have presented are not reported in the literature appears to indicate that they are very unusual. The cases have been too frequently encountered over a period of several years to believe that this is true. From conversation with a number of physicians who see a large range of clinical material I have learned that closely parallel cases are occasionally seen. I must conclude that the significance of the described type of sublingual inflammation has been overlooked or its existence has been considered not sufficiently important to report.

SUMMARY

A group of cases of sublingual gland inflammation in otherwise healthy children is presented, differing in clinical picture and in etiology from the hitherto described acute nonepidemic lesions of these glands. The usual causes of acute inflammation of the sublingual glands are not in evidence.

The characteristic features are: Sudden onset of sublingual and median submental swelling with mild febrile manifestations; scattered red spots in the mucous membrane over the sublingual swelling, interpreted as inflamed orifices of the sublingual ducts; rapid increase in size, often to grotesque proportions, of the moderately painful submental swelling, frequently accompanied by pronounced reddening of the overlying skin; early recession of the sublingual swelling, contrasting with persistence of the submental tumor for one to three weeks; fever slight and general condition good throughout the course; no complications, sequelae, or recurrences.

1275 Madison Avenue.

A PROTECTIVE THERAPY FOR MUMPS*

ALFRED F. HESS, M.D.
NEW YORK

The protection afforded to man against epidemic diseases through the employment of prophylactic antiserum injection is of course best illustrated by the case of diphtheria. It is likewise known that many infections to which animals are subject can be prevented by a similar form of passive immunization. While the number of experimental infections which can be prevented in this manner is not large, it is a notable fact that the blood of animals which have recovered from hog cholera carries a protective principle capable of warding off, for a time, infection with the filterable virus of that disease.

That human blood of one individual can be injected safely into another individual is of course a commonplace. Recent experience with the transfusion of large quantities of blood is convincing in establishing the value and safety of this procedure. Experience has also shown that human blood carrying immunity principles can be employed as therapeutic agents in several infectious diseases in man. Thus McKenzie and Martin[1] employed the blood serum taken from patients who had recovered from epidemic meningitis in the treatment, by intraspinal injection, of similar cases of meningitis. The blood taken from patients who have recovered from scarlet fever has also been employed,[2] and apparently with advantage, in the treatment of severe toxic cases of scarlet fever. Flexner and Lewis[3] have shown that the blood serum derived from monkeys or human beings who have recovered from epidemic poliomyelitis is capable of preventing in monkeys the paralysis which follows the intracerebral injection of the poliomyelitis virus, and Netter[4] has employed the serum taken from recovered human beings for the treatment of patients with acute poliomyelitis by intraspinal injection.

It is obvious, therefore, that the employment of the blood of one individual as a therapeutic agent for another is a method which in

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1. McKenzie and Martin: Brit. Med. Jour., Oct. 31, 1908, p. 1341.

2. Reiss and Jungman: Deutsch. Arch. f. klin. Med., 1912, cvi, Nos. 1 and 2. Reiss: Therap. Monatsh., 1913, xxvii, No. 6.

3. Flexner, S., and Lewis, P. A.: Experimental Poliomyelitis in Monkeys, Jour. Am. Med. Assn., Aug. 20, 1910, p. 662.

4. Netter, E.: Bull. de l'Acad. d. l'Acad. d. méd., 1914, lxxviii, 523.

itself is without danger, and, under certain circumstances, offers advantages to the patient to be secured in no other way. Such small objections to the employment of blood as a therapeutic agent as exist can be obviated by the selection of suitable donors.

In view of these considerations it is interesting to consider what may be accomplished in preventing mumps, or epidemic parotitis, especially in institutions in which a large number of cases arise from time to time. Mumps is still to be ranked among the highly contagious infective diseases of unknown etiology, the specific causative microbic

TABLE 1.—DATA OF DONORS AND OF INJECTED PATIENTS

Donor	Age	Date of Mumps	Donee	Age	Date of Inoculation	No. c.c. Injected
1. S. C.	5½	1/30/15	H. S.	4	2/1/15	6
2. P. F.	4	1/30/15	B. K.	4	2/1/15	6
3. G. D.	4	1/31/15	S. G.	4	2/1/15	8
4. A. S.	5⅓	1/29/15	P. K.	3	2/1/15	6
5. I. R.	4	1/22/15	Y. G.	3½	2/1/15	6
6. J. S.	4	1/22/15	F. G.	3½	2/1/15	8
7. R.	6⅓	1/22/15	E. Z.	2½	2/2/15	7
8. H. H.	5	1/22/15	R. G.	2½	2/2/15	8
9. S. G.	5⅓	1/22/15	M. H.	4	2/2/15	6
10. G.	5	1/23/15	D. E.	3¼	2/2/15	6
11. M.	2½	1/23/15	S. S.	2¼	2/2/15	8
12. R.	4½	1/23/15	H. L.	2	2/4/15	6
13. K.	3½	1/24/15	D. G.	2	2/4/15	6
14. S.	3½	1/25/15	H. I.	3	2/4/15	6
15. M. G.	4	4/ /14	B. Z.	2¼	2/4/15	6
16. D. G.	5	4/ /14	I. S.	1½	2/4/15	8
17. L. S.	5	4/ /14	H. C.	1⅔	2/4/15	6
18. B. K.	6½	3/ /13	S. G.	5½	2/4/15	6
19. J. S.	5½	12/ /12	L. S.	4½	2/4/15	8
20. L. S.	2⅓	12/ /12	L. S.	5½	2/4/15	6

agent not having been discovered. The disease is, however, one in which one attack yields protection that is general and persistent. The question arises, therefore, whether the blood of persons who have recovered from one attack of the disease does not contain immunizing and protective principles which can be employed in the protection of other exposed persons. Since the collection and the injection of the blood, as indicated above, are readily carried out, an effort was made this winter to control by this means an epidemic of mumps prevailing in the Hebrew Infant Asylum, which for the second time in two years was visited by a severe epidemic. The epidemic was well under way when we determined to undertake this prophylactic therapy, as may

be seen from Table 2, which shows the cases as they developed in the various wards, both previous and subsequent to the injections. At the time treatment was begun, about forty cases of mumps had broken out in the institution within the past month, and, as Table 2 shows, new cases were developing almost daily. The conditions surrounding an institution of this kind are peculiarly favorable for judging the effect of prophylactic treatment of the various infectious diseases, as most of the children are admitted during infancy, and we have complete knowledge of the infectious diseases which they have contracted while under our care.

TABLE 2.—OCCURRENCE OF MUMPS IN WARDS BEFORE AND AFTER INJECTIONS

Date	Ward No.				
	4	6	10	11	12
Jan. 22	1	6	1	1	0
Jan. 24	0	0	0	0	1
Jan. 25	1	0	0	0	0
Jan. 26	2	3	0	0	0
Jan. 28	0	0	0	0	1
Jan. 29	0	0	1	0	0
Jan. 30	2	1	0	0	1
Jan. 31	0	1	0	2	1
Feb. 8	0	1	1	1	0
Feb. 10	0	0	1	1	0
Feb. 11	1	0	0	2	4
Feb. 14	2	1	0	1	4
Feb. 15	3	0	0	0	1
Feb. 17	2	0	0	0	1
Feb. 20	3	0	0	0	0
Feb. 22	2	0	2	1	0
Feb. 23	0	0	0	1	0
Feb. 25	0	1	3	1	0
Mar. 2	0	0	0	2	2
Mar. 3	0	1	0	1	1
Mar. 4	1	0	0	0	0
Mar. 7	0	0	0	0	0
Mar. 18	0	0	0	0	0

* Horizontal lines indicate period when injections were begun in the different wards.

Twenty children were given protective injections. They were, for the most part, children who had entered the institution before the age of one year. Naturally, none were injected who had had mumps in the course of the epidemic of the winter of 1912-13 and who had acquired immunity in this way. The ages of these children, as well as of the donors, and the amount of blood injected, may be seen in Table 1.

Whole blood was used and was injected at once intramuscularly.[5] The donors form three groups: The first includes children, four in number, who were just recovering from mumps; the second comprises ten children who had recovered from the disease about ten days previously; there is a third group, composed of six children who had had mumps one or two years before. It should be added that the results of the treatment in the last group cannot be considered convincing, in that three (15, 16 and 17) must be entirely left out of consideration, as they did not happen to come in contact with active cases of the disease, and because the other three (18, 19 and 20) had been in the institution

TABLE 3.—INCIDENCE OF MUMPS AMONG INJECTED AND NONINJECTED CHILDREN

Ward No.	Total Census	No. of Susceptibles	Inoculated Cases	Date Transferred to Ward	No. Cases Developing Mumps Subsequently		Remarks
					Not Inoculated	Inoculated	
4	25	22	3 (Nos. 1, 12, 14)	2/15/15	11	0	Nine cases of mumps removed from this within previous three weeks.
6	30	19	1 (No. 13)	2/11/15	8	0	Twelve cases removed.
10	30	27	1 (No. 20)	2/15/15	5	0	Four cases were removed from this ward within previous three weeks.
11	34	32	2 (Nos. 18, 19)	2/15/15	7	0	Six cases were removed within previous three weeks.
12	34	34	10 (Nos. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11)	2/12/15	13	0	Ten cases were removed within previous three weeks.

but six weeks, so that we did not possess first-hand knowledge as to their susceptibility to mumps. As was to be expected from the experience of others, there were no disagreeable manifestations following the injections—neither a rise of temperature nor local reaction. The epidemic was so widespread that only three of the children under treatment did not come into contact with the disease. There are therefore seventeen who must be regarded as having been not only susceptible,

5. The blood was aspirated in the usual way and immediately injected into the patient. The procedure required so short a time that there was no need of adding any anticoagulant, and there was no disturbance due to premature clotting.

but also exposed to mumps. It is therefore striking to note that among these seventeen, none contracted the disease. That the injections were effective in bringing about this result may be seen from a glance at Table 3, which shows that in the wards where the children were not protected by injection, fully one-third, or even one-half, came down with the disease.

Our results hardly seem to require extended comment. We may add, however, that by means of these injections we were able, in a large measure, to check the epidemic. It would seem that preventive treatment of this kind could well be carried out in institutions for children, and that this simple procedure might likewise be resorted to in the home where one or more children are exposed to infection. Our experience seems to indicate that the blood may, with advantage, be obtained from the donor even before the parotid swelling has disappeared, and that it possesses protective principles at this early stage. As is well known, the incubation period of mumps is long, about eighteen days, so that it is possible to resort to protective injection some days following exposure. It is naturally impossible to state the duration of immunity acquired in this way; but it seems reasonable to believe that it well outlasts the usual danger period of infection. This type of therapy probably can be resorted to in connection with epidemics of other infectious diseases, for example, measles, in which one attack confers a marked immunity.

16 West Eighty-Sixth Street.

PARAPHARYNGEAL ABSCESS AS DISTINGUISHED FROM RETROPHARYNGEAL AND PERITONSILLAR ABSCESSES *

HENRY HEIMAN, M.D.
NEW YORK

Ordinarily a retropharyngeal abscess is easily diagnosed, an incision made from within the mouth, the pus evacuated, and an uninterrupted recovery results. In some cases, however, where there is only a retropharyngeal adenitis, no pus may be obtained by the first incision, but may be obtained later when the adenitis has broken down; or, again, the patient may recover without a second operation. In still another class of cases, incision yields little or no pus, the symptoms of fever and pain on swallowing continue, the patient becomes more septic in appearance, the tumefaction seen from within the oral cavity remains the same, while the external swelling usually increases in size. In these cases, the signs may continue unabated or may become progressively worse for weeks, even after repeated, usually unsuccessful, incisions from within the mouth, until a deep external operation is made, when, as a rule, considerable pus is evacuated and the patient recovers. It is with the view of describing, classifying, and attempting to clarify in our minds this last mentioned type of cases that this paper has been written.

History.—In 1903 Broca[1] described two cases of "peripharyngeal" abscess, with acute history, spontaneous rupture, and cure, in infants, one 6 months and one 9 months of age. He says that almost all acute "peripharyngeal" abscesses are "adenophlegmons" and involve the chain of glands along the carotid sheath, as distinguished from those in front of the prevertebral muscles.

Since then Broca, Swain and others, have written more or less extensively on this subject. Further elucidation, however, especially as regards the clinical distinctions between lateral pharyngeal abscess and conditions simulating it, and also as regards the proper method of treatment, may not be amiss. In this paper this type, i. e., the "peripharyngeal" abscess of Broca, is known, for reasons to be mentioned later, as parapharyngeal abscess.

The retropharyngeal space is limited above by the base of the skull, while below it extends behind the esophagus and is continued into the

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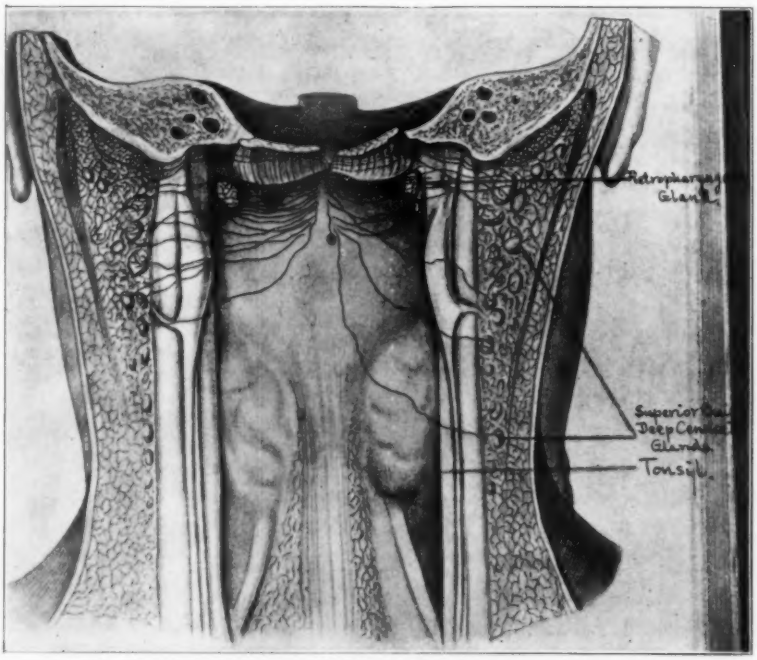
* Read before the American Pediatric Society at Lakewood, N. J., May 24, 1915.

1. Broca, M.: Abcès pèri-pharyngiens, Bull. méd., Paris, 1903, xvii, 579.

posterior mediastinal cavity of the thorax. The lymphatics of this region, as seen by the accompanying illustration from Most,[2] consist of two sets of glands, viz.: (1) the retropharyngeal glands, (2) the deep cervical glands.

1. The retropharyngeal glands, small and few in number, forming a chain on each side of the median line, are found in the buccopharyngeal fascia, posterior to the pharynx and anterior to the arch of the atlas, from which they are separated by the prevertebral muscles. They receive the lymphatic drainage from the nasal cavities, the nasopharynx, and the auditory tubes. These glands atrophy in early child-



The lymphatics of the retropharyngeal space.

hood; it is extremely rare to find them after the second or third year of life. Most has never observed these glands in autopsies on older children or in adults. It is these glands from which the retropharyngeal abscesses originate.

2. The deep cervical glands, numerous and of large size, form a chain extending along the course of the internal jugular vein and the internal carotid artery, by the side of the pharynx, esophagus, and

2. Most, A.: Zur Topographie und Aetiologie des retropharyngeal Drüsenabscesses, Arch. f. klin. Chir., 1900, lxi.

trachea; and extending from the tip of the mastoid to the root of the neck. They are divided into two groups, the superior and inferior. It is the superior group which interests us in this paper. This superior group drains the mouth, tonsils, palate, pharynx, tongue, posterior part of tongue, nasal fossae, interior of skull, and the deep parts of the head and neck. It is this set of glands that forms the lateral columns of the pharynx, inflammation of which causes parapharyngeal abscess, or the "adenophlegmon" of Broca.

Etiology.—It will be readily understood, from an anatomic point of view, how any inflammation of the rhinopharyngeal mucous membrane may be followed by a parapharyngeal, as well as a retropharyngeal abscess. Although the etiology of both conditions is practically the same, it is our observation that the retropharyngeal type is most likely to occur after the ordinary rhinopharyngitis, while the parapharyngeal type usually follows influenza, tonsillitis, scarlet fever, measles and other infectious diseases.

Occurrence.—Retropharyngeal abscesses occur nearly always in infancy, as the retropharyngeal nodes are supposed to atrophy after the third year of life. Most observers report the occurrence of two-thirds to three-fourths of their cases in children under 1 year of age. The so-called retropharyngeal abscess secondary to tuberculous spinal caries may occur in later childhood, even in adult life; but it is possible that the adult cases described in the literature as examples of true retropharyngeal abscess may have been cases of cellulitis or of involvement of the lateral pharyngeal glands. The parapharyngeal abscesses, involving as they do the lateral lymph chains of the pharynx, are more common after the age of 3, and probably occur more frequently than we suppose, owing to the fact that they may be mistaken for the ordinary retropharyngeal variety.

Symptoms.—The early symptoms of parapharyngeal abscess are those of a mild inflammation of the pharynx, occurring usually in the course of one of the infectious diseases. These may be so slight as to give no indication of the diagnosis. Then suddenly the temperature may rise to 102 or 103 F. and continue, septic in type, for several days, with no marked local signs apparent. Discomfort, difficulty in swallowing and thickness of speech usually occur. There may then appear a swelling internally just lateral to the tonsil, or externally just below the angle of the jaw and in front of the sternocleidomastoid muscle. There is seldom edema of the uvula or pharynx. The tonsil is seen to be displaced toward the median line. With this exception and the possible appearance of the internal, lateral mass, the pharynx itself may look absolutely normal. The temperature and prostration continue until the pus is evacuated externally, from which time there is, as a

rule, an uninterrupted recovery, unless the prolonged illness has exhausted the patient.

Differential Diagnosis.—So-called parapharyngeal abscess must be differentiated from several conditions simulating it, viz.: (1) Retropharyngeal abscess, (2) peritonsillar abscess, (3) interstitial or tonsillar abscess, (4) cervical adenitis occurring in the course of the various infectious diseases.

1. From retropharyngeal abscess. In our opinion, there is little doubt that the variety of abscesses we have styled parapharyngeal, because their site is by the side of, or lateral to the pharynx, exists as a separate entity and may be distinguished from the retropharyngeal type. The retropharyngeal abscess may produce a central bulging, though usually somewhat lateral to the midline; it does not displace the tonsil; it is as a rule accompanied by edema of the pharynx and uvula, by a brassy voice, with the symptoms of more or less laryngeal stenosis, and at times by a retraction of the head. On palpation a distinct cushionlike feeling or fluctuation may be obtained. The parapharyngeal abscess produces bulging nearer the lateral pharyngeal wall, if at all internally, but rarely in the midline; it nearly always displaces the tonsil—and this is a very important point in diagnosis—*toward* the median line, and is rarely accompanied by any marked local change in the appearance of the pharynx, or by any symptoms of pressure on the larynx. In the case of retropharyngeal abscess, internal incision usually cures, unless the suppuration extends to the lateral columns of the pharynx, at which stage the retropharyngeal becomes a parapharyngeal abscess and then requires an external incision, or burrows its way into the mediastinum. The retropharyngeal abscess is usually diagnosed early, while the parapharyngeal abscess may progress for one or two weeks before a diagnosis is made, or before the external swelling becomes sufficiently prominent to justify an external incision. Of importance also in the differential diagnosis is the age of the patient As the retropharyngeal glands atrophy before the child is 3 years of age, an abscess in this region in a child over this age is more likely to be of the parapharyngeal form.

2. From peritonsillar abscess.

In peritonsillar abscess there is marked redness of the soft palate, and a swelling above and to the inner side of the tonsil, pushing forward the anterior pillar of the fauces. This abscess points within a few days and ruptures spontaneously or requires incision. The tonsil is not usually displaced inward as in the parapharyngeal type; the course is not a matter of weeks, as in some cases of parapharyngeal abscess and there is no external swelling.

3. From interstitial or tonsillar abscess.

These abscesses may follow a severe tonsillitis, involve the tonsils alone, rarely the contiguous tissues, and as a rule do not push the tonsil towards the midline. They cause a marked tumefaction of the tonsil itself, but never an external fluctuating mass.

4. From cervical adenitis occurring in the course of the infectious diseases.

Scarlet fever, influenza, measles, diphtheria, and tonsillitis are often complicated by acute inflammation of the superficial glands of the neck. The glands involved comprise, in practically all cases, the chain known as the superficial cervical glands, although rarely the process spreads to the deeper lymphatic structures. There is as a rule, no suppuration and consequently slight prostration; and lastly there is never any pushing inward of the tonsil—the most characteristic feature of the parapharyngeal abscess.

Treatment.—There is little to be said about the treatment of parapharyngeal abscess, except that repeated internal incisions so often fail to cure, that an external operation with drainage, as soon as the diagnosis is made, is, in our opinion, the ideal method. The rationale of the surgical procedure is evident, if one considers the anatomic relations of the superior chain of the deep cervical glands. The pus cannot burrow its way inward, owing to the resistance of the pharyngeal fascia, nor downward, on account of the dense capsule of the gland, and consequently it must point toward the plane of least resistance, which is externally, owing to the entrance of the glandular vessels at this site.

Brief abstracts of three cases of typical parapharyngeal abscess operated on by Dr. A. A. Berg follow:

CASE 1.—B. G., aged 4½ years, female. Patient had tonsillitis for several days. After this had subsided the temperature continued high, from 102 to 104 F. for two weeks. The gradual formation of an abscess was observed, which pushed the tonsil inward and produced also an external fluctuating mass. There was mild prostration, thickness of speech, and some difficulty in swallowing. There were no brassy cough, laryngeal stridor or other symptoms of retropharyngeal abscess. After an external operation the patient rapidly recovered.

CASE 2.—R. G., aged 3½ years, male. Three weeks after the onset of a mild scarlet fever, a swelling of the right side of the neck just below the angle of the jaw was noticed. This continued, with fever, increasing difficulty in breathing and swallowing, for one week. The tonsil and contiguous tissues were considerably swollen; the tonsil itself was displaced towards the median line. Internal incision disclosed a slight amount of pus, but afforded only temporary relief. External incision and drainage were then done, with almost immediate relief and permanent recovery.

CASE 3.—A. B., aged 3 years, male. For ten days the patient had an intermittent type of fever, ranging from 101 to 104 F., with malaise, prostration, mild cough, and rhinitis. A diagnosis of influenza was made. At the end of the first week dyspnea, dysphagia, and a swelling on the right side of the neck

were noticeable. The pharynx was only slightly reddened; there was no edema of the pharynx or uvula. There was a distinct swelling lateral to the tonsil, which appeared to displace it in the direction of the midline. The external swelling increased in size for several days, until an external incision was made, with evacuation of the pus and a subsequent gradual recovery.

CONCLUSIONS

1. There occurs, especially in children, a form of abscess which is occasionally mistaken for a retropharyngeal abscess, but which has a separate and distinct entity. It may be called a parapharyngeal abscess, as its site is in the lateral columns, that is, by the side, of the pharynx.

2. The origin of this abscess is from the superior chain of the deep cervical glands, which are situated along the course of the carotid artery, as distinguished from the retropharyngeal glands, situated in the circumscribed retropharyngeal space, just lateral to the midline and in front of the prevertebral muscles.

3. These abscesses are as a rule cured only by external operation.

64 West Eighty-Fifth Street.

PROGRESS IN PEDIATRICS

DYSENDOCRINISM IN CHILDREN

MARK S. REUBEN, M.D.
NEW YORK

INTRODUCTION

In spite of the fact that our knowledge of the internal secretions is rudimentary and confused, great progress has been made during the last ten years in dispelling the uncertainty which surrounds their function both in health and in disease. Everyone must be convinced that these organs are second to none in the body in their influence on physiology, pathology and clinical medicine. Disturbances in the internal secretions are responsible for anomalies of growth and morphogenesis, for disturbed nutrition, disturbed excitability of the nervous system, for loss of resistance to infection and intoxications; they are also responsible for certain dyscrasias and morbid temperaments; and the equilibrium of the nervous system, especially the sympathetic, is also maintained by the internal secretions.

Johannes Müller (1844) and Ruysch showed that the blood received secretions from internal glands. The term "internal secretions" was first used in 1855 by Claude Bernard, who described the glycogenic function of the liver as the *"sécrétion interne,"* while he referred to the preparation of bile as the *"sécrétion externe."*

It was Berthold of Göttingen who in 1849 first demonstrated by means of experiment, the nature of the activity of a true ductless gland: he showed the influence which can be exerted on the composition of the blood, and thus on the entire organism, by an organ through which the blood stream circulates. He removed the testicles from cocks, and grafted them on another part of the body; he found that the animals remained male in regard to the voice, reproductive instinct, fighting spirit, and growth of comb and wattles.

In 1889, Brown-Séquard, then 72 years of age, described experiments which he had carried out on himself, by the subcutaneous injection of testicular extracts. This really marked the birth of the doctrine of the internal secretions.

The first endocrinous active principle chemically isolated (in 1897) was the hormone of the adrenal medulla, which was given to the world by Abel and Crawford.

The hormone theory originated with Bayliss and Starling in 1902. They discovered that if an extract of the duodenal epithelium is injected into the blood stream a rapid flow of pancreatic juice is

determined; these observations rendered it clear that this flow of pancreatic juice must be regarded as due to the absorption of some internal secretion into the blood. To the active substance which is yielded by the epithelium cells of the duodenal mucosa they gave the name of "secretin." A similar but not identical internal secretion has been shown by Edkins to be produced by the cells of the mucous membrane of the pyloric end of the stomach. To such stimulating substances as that contained in the extract of the duodenum the term "hormone" (ὁρμάω = to stir up) was originally applied by Starling, and the expression has been extended to include the active principles of all internal secretions. Schäfer distinguishes between hormones which promote the activity of another ductless gland and those which have an inhibiting influence. To these latter he applies the term "chalones" (χαλάω = to make slack) and to the former he refers as "hormones." A chalone may therefore be defined as an endocrine product which inhibits or prevents the activity of an organ as distinguished from a hormone, which excites the tissue to increased activity; for both these substances he employs the general term "autacoid substances" (αὐτός = self ἄκος = remedy).

According to Vincent the process of internal secretion consists in the preparation and setting free of certain substances of physiologic utility (the raw materials for which are supplied by the circulating blood) by certain cells of a glandular type; the substances set free are not passed on to a free surface but into the blood stream. Organs which are not known to possess any other function than that of passing such material into the blood or lymph are termed "internally secreting" or "endocrine" organs (ἔνδον = within κρίνω = to separate). An endocrine organ may be a special organ (thyroid), a special structure of another organ (pancreas), or it may be neither special structure nor special organ, as the cells which secrete prosecretin, seem to be the ordinary cells which line the mucosa and extend into the glands.

The active materials of the internal secretions are for the most part not rendered inactive by prolonged boiling; they are dialyzable, and act readily on the cells which they influence.

The endocrine organs, although autonomous in their action, are to some extent influenced by the nervous system, and in turn their autocoids have a tremendous influence on the nervous system; many of the symptoms of dysendocrinism are due to irritation of the nervous system (especially the sympathetic) by abnormal secretions or by normal secretions in an abnormal way (hyposecretion or hypersecretion). The adrenals seem to be most influenced by the nervous system, and the gonads least. Stimulation of a certain spot in the floor of the fourth ventricle, and also at a spot in the regio subthalamica leads to increased secretion of epinephrin.

Langley divides the vegetative nervous system into two categories, the craniosacral and the sympathetic. In the autonomic nervous system he includes both the craniosacral autonomic nerves (parasympathetic system) and the sympathetic system. Many other writers, however, include only the craniosacral system in the autonomic nervous system and differentiate this system both anatomically and physiologically from the sympathetic system. The action of these two systems of nerves on the different organs which they innervate is antagonistic; for example, the sympathetic nerve accelerates the heart whereas the autonomic vagus nerve slows it.

Modern pharmacology regards as antagonists the sympathetic and the autonomic nervous system. Epinephrin is a specific stimulant of the sympathetic system by its action on the myoneural junction; pilocarpin and muscarin are specific irritants of the autonomic system. Administration of thyroid produces symptoms which simulate those of pilocarpin and muscarin, as, sweating, diarrhea, disturbances in respiration, lymphocytosis, and eosinophilia. Atropin is an antidote for pilocarpin and it also produces symptoms opposite to those of thyroid extract. It has now been attempted, on the basis of these physiologic facts, which indicate that from the thyroid gland impulses may be sent out along the tracts of the sympathetic as well as the autonomic system, to distinguish the symptoms of Graves' disease which might be due to irritation of the sympathetic, from those which might be attributed to autonomic stimulation.

DEVELOPMENT

It is well known that the adrenals consist of two parts, which, although anatomically united in man, are morphologically distinct and are developed from different embryonic formations. The cortex is formed from mesoderm cells of the genital ridge; the medulla is developed from cells which belong to the same neuroblast masses as give rise to the nerve cells of the sympathetic ganglia. In fishes these parts remain separate, forming "the interrenal bodies," which represent the cortex of the mammal, and the paired chromaffin bodies, which represent the medulla. In all higher vertebrates the two parts are united into one organ; it is only in mammals that the same condition is found as in man, viz., a central medulla with an enclosed cortex.

The infundibulum of the pituitary is composed of nervous tissue and expands in the interior of the gland into the pars nervosa. The anterior lobe is formed by a pouchlike outgrowth of the buccal ectoderm (Rathke's pouch). The posterior lobe is of neuro-ectodermic origin; the pineal gland, like the posterior lobe, is also of neuro-ectodermic origin.

The thyroid is found in all vertebrates; it is developed by a median outgrowth from the entoderm lining the floor of the pharynx at a level between the first and the second branchial arches. The parathyroids are developed from outgrowths of the third and the fourth visceral clefts on either side. The thymus is of entodermal origin and arises from the third branchial arch. The pancreas and the mucosa of the small intestine arise from the intestine and are therefore also of entodermal origin.

The gonads arise from the genital ridge, and are therefore, like the adrenal cortex, of mesodermal origin.

It appears that the glands which have a common origin are related in function; thus epinephrin and pituitary extract seem to have the same action; the anterior lobe of the pituitary and the thyroid, both of same origin, are related in function; and finally the adrenal cortex and the gonads, both arising from the mesoderm, are associated in the development of the secondary sex characteristics.

EXPERIMENTAL DATA

Total removal of the pituitary in adult dogs causes death in two or three days with symptoms of cachexia hypophysipriva. In puppies death does not follow for ten days (3-20). The symptoms of cachexia usually do not appear for from twenty-four to forty-eight hours after the removal of the gland; a marked diminution of urinary output even to anuria and a transient glycosuria may occur immediately after operation in adult dogs; and in puppies a postoperative polyuria has been observed, contrasting with the opposite condition seen in adult dogs. The symptoms of cachexia are unsteadiness of gait and lowered body temperature; an awkward arching of the back, with incurvature of the tail is characteristic; later there is still further fall of temperature, slow respiration, slow pulse, irregular muscular contractions, tremors, lethargy, anesthesia, coma and death; the temperature before death may fall 20 degrees C. Grafts in cases of total removal cause a distinct prolongation of life through this means.

The effects of posterior lobe removal are inconclusive; some of the dogs have convulsive attacks with maniacal excitement and persistent erotomania.

The results of partial removal of the anterior lobe are the same if the posterior lobe is removed also. In puppies such removal leads to infantilism. The animals remain undersized and the secondary sexual characteristics do not develop; there is also a tendency to hypotrichosis and to subnormal temperature. In adult dogs partial removal causes adiposity, sexual degeneration, subnormal temperature, hypotrichosis, polyuria and somnolence or restless playfulness.

Total removal of the anterior lobe causes death in sixty-eight hours with symptoms of cachexia; the consequences of stalk separation are equivalent to total or nearly total hypophysectomy.

They also found that repeated injections of the entire gland cause a rapid loss of weight in puppies and in adult dogs; in cases of anterior lobe insufficiency injections of anterior lobe extract cause a thermic response (from 2 to 4 C.).

The occasional appearance of glycosuria after hypophysectomy had led these observers to further study along this line. They noticed that removal of the posterior lobe and part of the anterior lobe causes a primary fall and a subsequent rise above the normal in the assimilation limit for sugars; that removal of part of the anterior lobe, however, produces little or no alteration in the carbohydrate assimilation limit; the removal of posterior lobe alone causes no primary glycosuria, unless there is considerable traumatism of the stalk, but there is an increased sugar tolerance; this increased tolerance can be brought down to normal by giving posterior lobe extract, 1/20 gm. subcutaneously, 1/80 gm. intravenously; or 2/5 gm. by mouth. In man the normal limit for glucose by mouth is 150 gm., and for levulose 100 gm. It will be seen that in case of posterior lobe insufficiency there is an increased sugar tolerance; such patients can take as much as 400 gm. of glucose without appearance of glycosuria.

To summarize, we may say that total removal of the gland, or total removal of the anterior lobe, causes death in two or three days, with symptoms of cachexia. Anterior lobe insufficiency in puppies caused adiposity, skeletal infantilism and failure in appearance of the secondary sexual characteristics; in adult dogs anterior lobe insufficiency causes adiposity and sexual degeneration. The symptoms of posterior lobe insufficiency are increased sugar tolerance, subnormal temperature, hypotrichosis, dry skin, low blood pressure, adiposity and large appetite.

RELATION OF DIABETES INSIPIDUS TO DYSPITUITARISM

It has long been recognized that polyuria with the appearance of dextrose in the urine is a not infrequent accompaniment of acromegaly; but it is only within the last year that both experimental and clinical evidence has accumulated to prove that diabetes insipidus is probably due to disturbed secretion of the pituitary.

In 1674 Thomas Willis first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. Claude Bernard discovered his so-called diabetic center in 1849; this point is situated in the floor of the fourth ventricle, between the centers of the pneumogastric and the auditory nerves; puncture at a point a little lower

causes simple polyuria, while puncture at a point a little higher in the frontal direction causes albuminuria.

Cushing found that after certain experimental manipulations of the canine hypophysis, a postoperatixe polyuria was of frequent occurrence; in adults oliguria rather than diuresis follows a total extirpation; in younger animals there was diuresis. On the other hand, in a series of partial extirpations, postoperative polyuria was almost always observed. Experiments support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. Schäfer found that posterior lobe substance given by mouth increases the urinary output; the experimental polyurias have therefore been brought about either by direct hypophysial insult, by the injection of extracts, or by glandular implantations. A hypophysial diuresis may also be elicited by nerve stimulation.

A review of the clinical histories included in many of the past articles on diabetes insipidus makes it clear that a large percentage have shown symptoms found in lesions involving the base of the brain, a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. Fuchter and Frank have emphasized the surprising frequency with which cases of primary optic atrophy, often with bitemporal hemianopsias which accompany the encephalic polyurias, are classified as diabetes insipidus. Kohler in seven of his twenty-two cases of diabetes insipidus found an affection of the infundibulum; Oppenheim in thirty-six patients with basilar luetic meningitis observed polyuria in twelve; Kruse in thirty-four cases of bitemporal hemianopsia noticed diabetes insipidus in seven cases; Oppenheim in two cases of general cerebral symptoms with double temporal hemianopsia and diabetes insipidus found on necropsy a gumma in the region of the chiasma in one case, and a gummatous meningitis in the region of the chiasma in another; in 1882 Hagenbach found a tubercle in the infundibulum of a girl (4½ years old) who had suffered a good deal from thirst and polyuria; in 1903 Rosenhaupt reported a case of diabetes insipidus in which a sarcoma of the anterior lobe of the hypophysis was found; in 1913 Frank reported a case of diabetes insipidus, due to a metastatic carcinoma of the hypophysis, and Simmond reported a case due to a gunshot wound of the hypophysial neighborhood. The evidence, both experimental and clinical, is therefore in favor of the view that diabetes insipidus is probably a manifestation of dyspituitarism.

EFFECTS OF EPINEPHRECTOMY

Extirpation of both adrenals is followed by death within from twenty-four to forty-eight hours; careful removal of one adrenal is seldom fatal. If the second adrenal is extirpated some time after the

first, no effect is at first apparent; later the animal becomes less lively and exhibits signs of muscular weakness; temperature becomes lowered; weakness becomes extreme; the pulse feeble, blood pressure low, and the respiration dyspneic; death soon follows, sometimes immediately preceded by convulsions.

EFFECTS OF THYROIDECTOMY

Thyroidectomy produces the most marked results in young animals. There is arrest of growth, especially of the skeleton, the cartilage bones long remaining incompletely ossified. Development of the generative organs is much delayed. The integument is swollen, the surface of the skin dry, the hair thin. The muscles are limp and weak; the highest functions of the nervous system remain undeveloped.

EFFECTS OF PARATHYROIDECTOMY

After complete parathyroidectomy most animals die from within a few days to a few weeks; the most acute symptoms are of a nervous nature. For the first day or two there is only anorexia; later there is exaltation of reflexes, with the occurrence from time to time of fibrillar contractions of muscles, and later cramplike and clonic contractions and eventually convulsive fits; the temperature may rise 2 or 3 degrees C. during the fit; there may be attacks of rapid gasping respirations and sometimes vomiting and diarrhea; death may occur within a few days or the affection may last a long time and spontaneous recovery may take place; this symptom complex is known as "tetania parathyreopriva." The parathyroids yield to the blood a special autacoid, of a chalonic nature which tends to prevent overexcitation. In animals which survive parathyroidectomy, changes in the growth and in the structure of the bones and teeth have been noted; in the teeth the calcification appears to be delayed and in the skeleton the bones generally remain smaller than in the controls; thus it is possible that these glands produce a second autacoid which is able to influence calcium metabolism; this is partly substantiated by the finding of an increased excretion of calcium in parathyroidectomized animals.

THYMUS

Extirpation of the thymus at the height of its development results finally in death; its most important function consists in the inhibition of acids and the consequent removal of injurious substances from the blood; it has a dominating position over the lymphatic apparatus. After thymectomy disturbances occur in calcium metabolism as well as changes in bone and in the central nervous system.

The results of thymectomy in animals which survive are:

1. The bones were generally distinctly softer and more pliable than in the control animals, and the thymectomized animals were more straddling and awkward in their gait.

2. The thymectomized animals showed less movement and less intelligence.

3. They also showed a distinct backwardness in weight.

4. Galvanic excitability of the peripheral nervous system is distinctly increased after extirpation of the thymus.

PANCREAS

In 1889 von Mering and Minkowski proved that the removal of the pancreas or even the greater part of the organ is immediately followed by hyperglycemia leading to a severe and fatal diabetes, whereas this effect is not obtained from mere ligature of the duct. The evidence for the action of an internal secretion which is yielded by the gland and which serves to maintain carbohydrate metabolism in a normal condition is very complete.

THE GONADS

It was shown by Leydig (1850) that the intertubular connective tissue is characterized by the presence of strands of epithelium-like cells; these have been termed the cells of Leydig, and collectively the interstitial gland of the testes.

If castration is performed in a child the secondary sexual organs remain undeveloped, and other male secondary sexual characters, such as growth of hair on the face and pubes, the enlargement of the larynx, and the development of the male characters of the skeleton, are arrested.

The ovary contains, besides the graafian follicles with their ova, follicular epithelium, and liquor folliculi, a highly vascular stroma formed of a peculiar connective tissue, firm in texture, and containing numerous spindle-shaped cells; these have been named the interstitial cells of the ovary and have been by some thought to be analogous to the interstitial cells of the testicle. The effects resulting from the removal of both ovaries are not so marked externally as in the similar operation in the male sex; if performed in young animals, it is not infrequently found that characters distinctive to the male are to some extent assumed; the uterus remains small; the external changes characteristic of puberty either do not occur or are greatly modified; there is no menstruation; a tendency to the male type of trichosis is often also exhibited.

Experimental evidence seems to point to the fact that the development of corpora lutea leads to the development of the mammae, the

secretion of milk, and to the hyperplasia of the uterus; its chief function seems to be related to the formation of the uterine decidua and the fixation of the embryo.

PINEAL

The most complete experiments yet made are those of Foà in the domestic fowl. In pullets in which the gland was destroyed no difference could be noticed on comparison with controls, but in cockerels Foà describes not only a more rapid growth of body but also an earlier development of the testicles and of the secondary sexual characters.

PHYSIOLOGIC ACTION OF ENDOCRINE EXTRACTS

PITUITARY EXTRACT

Extracts of pituitary have a remarkable influence on the vascular system, producing a great rise of blood pressure, with contraction of vessels. The effect on the blood vessels is a direct one; the effect on the heart is different from that of epinephrin, for whereas, with the vagi cut or paralyzed epinephrin causes marked acceleration of heart, pituitary extract causes a slowing of the heart with increased force of individual beats; renal arteries are dilated and there is an increased secretion of urine. This extract powerfully affects the uterus as well as the bladder and the intestine; it also produces dilatation of the pupil of the excised eye of the frog; the secretion of the mammary gland is increased; pituitary extracts cause the disappearance of glycogen from the liver and they facilitate the production of alimentary glycosuria by lowering the limit of assimilation of sugar.

EPINEPHRIN

Intravenous injection causes an immediate and marked rise of blood pressure, due to contraction of peripheral arteries; concomitant with this is a slowing of the heart's action; there is some diminution in the force of respiration; the arteries of the splanchnic area are the most affected; the cutaneous vessels are strongly contracted; it is always the smaller vessels which are most affected. Other involuntary muscular tissue supplied by sympathetic fibers is also affected, as spleen, vagina, uterus, vas deferens, retractor penis; muscular contraction of intestine, stomach and esophagus is inhibited; muscles of the eye are excited so that the eye tends to protrude and the palpebral fissure appears to enlarge; the third eyelid is retracted and the pupil widely dilated; a flow of saliva is produced; the lacrimal glands are caused to secrete; as a rule there is no increase of sweat secretion.

Locally epinephrin produces marked contraction of the muscular coat.

THYROID EXTRACTS

Intravenous injections produce (the most common effect) a marked but evanescent fall of blood pressure, dilatation of peripheral vessels and slowing of the heart. Given by mouth thyroid extract reduces blood pressure; large doses produce tachycardia, nervous excitability, flushing of skin, increase of perspiration and increase of nitrogen metabolism. If administration of thyroid is long continued the fat of the body is diminished and glycosuria may be caused; in extreme cases there may be exophthalmos and other symptoms referable to cervical sympathetic excitation, and dilatation of the pupil, psychical excitement, insomnia, tremors, and emaciation. The active substance is iodothyrin or the compound protein iodothyroglobulin. The former was prepared by Baumann (1895) and found by him to contain a marked amount of iodin (0.3-0.9) per mille of dry substance.

EXTRACT OF OTHER ENDOCRINE ORGANS

Pineal extract, like all other extracts except pituitary and chromaffin, contains depressor substances; later there is a prolonged rise, with dilatation of the kidney volume, and diuresis; there is some increase of contraction of the uterus. Pineal extract is slightly galactogogic.

Mammary extract leads to increased epinephrin in the blood; causes glycosuria, and may arrest development of the embryo, and cause abortion.

Extracts of placenta and fetus produce a chalonic autacoid which have an inhibitory effect on milk secretion.

PARATHYROID EXTRACTS

Ott found that when parathyroid extracts are given intravenously, the blood pressure is first raised, then lowered; rate of respiration is increased, diuresis is produced, and in large doses they have the effect of lowering the body temperature. Locally extracts have the power to increase the extent of contraction both in intestines and uterus and dilate the pupil.

DYSPITUITARISM

Vesalius was the first to describe the pituitary, and in his "De Corporis Humani Fabrica" he named it "glans pituitam excipiens"; he believed that this gland secreted the nasal mucus (pituita, phlegm). Galen many years before him knew of this gland, however, and judging from its well protected location thought it was of great importance to the human economy. In 1778, Soemmering described it more fully and called it "hypophysis cerebri." Both Vesalius and Soemmering were of the opinion that the pituitary is a gland; but as they could not

find any duct, they considered it a part of the nervous system. Wepfer, Bonnet (1679) and Morgagni found colloid cysts in the pituitary, and Greding (1771) and Melcrave observed and described enlargements of the pituitary. Wenzel claimed that diseases of the pituitary may cause epilepsy; in the light of present knowledge this is true, for many patients suffering from dyspituitarism have manifested epileptiform seizures.

In 1838 Rathke discovered the dual origin of this gland from the floor of the third ventricle and from a diverticulum of the pharynx (Rathke's pouch). In 1840, Mohr demonstrated the relation of adiposity to tumors of the hypophysis. In 1860, Liégeois, studying the anatomy of this organ, added it to the list of ductless glands. Marie and Marinesco reported two cases of acromegaly in 1886, and although they were mistaken, in that they thought this disease was due to hyposecretion of this gland, they were the first to draw attention to the relationship between this disease and changes in the hypophysis. About this time Launois described gigantism, and thought that some of these cases may be due to disease of the pituitary; but it was Cunningham who, in 1891, had proved that gigantism and acromegaly are the same disease, the only difference being that gigantism was the result of pituitary disease in cases in which the epiphyseal centers had not yet ossified, and acromegaly in cases in which ossification had taken place. In 1899 Oppenheim recognized the importance of roentgenoscopy of the sellar region as an aid in diagnosis of tumors of the pituitary. Although Pechkranz correlated adiposity with abnormal skeletal changes, with anomalies of the hypophysis, and although Babinski reported a case of tumor of the pituitary without acromegaly in 1900, Frölich is usually given the credit of describing this type of dyspituitarism, in spite of the fact that his communication did not appear until 1901. To Cushing (1909) is due the credit of putting our knowledge of the secretion of the pituitary on a scientific basis; it is he who pointed out and clearly stated the functions of the individual lobes and showed that clinically we may have many types, depending on whether one or both lobes are hyposecreting or hypersecreting. In 1912 Burnier collected a group of cases in which dwarfism is associated with hypophysial symptoms; he refers to them as cases of "hypophysial nanism."

Sir Victor Horsley was the first to publish a personal note regarding the experimental removal of the gland; the first actual contribution, however, was made by Marinesco (1892); he concluded that the loss of the whole gland was compatible with life for a long time. The first studies which include any suggestive observations on the symptomatology of a pituitarism were published in 1892, and in 1894 by

Vassale and Sacchi; among others who experimented were Cyon, Caselli, Friedmann, Maas, and von Eiselberg. The most important contribution was made in 1908 by Paulecco of Bucharest; he found that removal of the anterior lobe is equivalent to removal of the entire gland (that is, death in twenty-four hours); that loss of the posterior lobe led to no appreciable disturbances, and that separation of the stalk from the base of the brain amounted to a complete or nearly complete removal, as the case might be. In the same year (1908) appeared the notable work of Herring on the anatomy and histology of the pituitary.

The first operations on the hypophysis were by Horsley; the operative procedure in attacking the hypophysis has been studied on cadavers by Lowe and Koening, Jr., but has been cleared essentially by Schloffer, who also operated on the first patient on the Continent in March, 1907.

CLINICAL MANIFESTATIONS OF DYSPITUITARISM

In man the clinical manifestations are nearly the same as those found by Cushing in dogs; the symptoms resolve themselves into those due to (1) hyposecretion or hypersecretion or perversion of the secretion of the gland itself; (2) those due to increased cerebral pressure; (3) those due to the local pressure of the tumor, and (4) those due to the involvement of the other ductless glands.

Deficiency of anterior lobe in children leads to infantilism; there is inhibition of skeletal development. Hypersecretion of the anterior lobe leads to gigantism in cases in which the epiphyseal centers had not yet ossified, and to acromegaly in adults. That gigantism and acromegaly are closely related is evident from the observations of Sternberg; he found that 20 per cent. acromegalics are over 5 feet 10 inches in height, and that 40 per cent. of all giants have some signs of acromegaly. In hyperpituitarism there is hypertrophic alteration of the skin, and increase in size of the hair follicles; there is also hypertrophy of the papillae and activation of the secretory glands, so that the skin becomes greasy and moist; hypertrichosis is marked. Deficiency of posterior lobe is usually associated with adiposity and increased sugar tolerance; the temperature is usually subnormal, and the subjective chilliness and drowsiness indicate diminished metabolism. The skin is usually smooth—may even suggest edema, but does not pit. The hair on the scalp may be abundant, but axillary and pubic hair may be entirely wanting; the nails are often small and do not show the crescent at their base. Constipation is often obstinate and usually improves on glandular therapy. Psychic disturbances are frequent and are usually due to involvement of frontal and temporal lobes. The symptoms of cerebral involvement are change in disposition, enfeeble-

ment of memory, disorientation and ". . . notable always is the utter lack of appreciation of, and complete indifference to, the existing condition." In hyperpituitarism, temperamental changes, wakefulness, lack of concentration and irritability are more common; in hypopituitarism mild psychoses to extreme mental derangements with epilepsy are not infrequent. The symptoms of increased cerebral pressure are too well known to need any detailed mention here; they are, in general, headache, general convulsions, double optic neuritis, and optic atrophy, change of position and of mental power, vomiting, vertigo, change in the pulse rate and attacks of syncope.

One of the most important local symptoms is primary optic atrophy; later there is superimposed optic neuritis due to the growth reaching a large state.

Among the most important of the local symptoms is deformation of the sella turcica; extreme hypersecretion and hyposecretion may exist with little if any alteration in the shadow cast by the bony encasement of the gland; the sella may be well preserved, even though the tumor may be enormous and has been of long duration. There are three types of sella deformation; (1) those associated with the thickening of the clinoids and dorsum sellae, (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of all outlines. Equally important are the abnormally small sellae, which accompany the primary glandular hypoplasias of the young.

The following symptoms present in dyspituitarism are referable to secondary involvement of the other ductless glands: imperfectly acquired secondary sexual characteristics in cases in which the lesion antedates puberty, and of resultant amenorrhea or impotence with retrogressive sexual changes, when the malady develops after the acquirement of adolescence; pigmentation of the skin, asthenia, low blood pressure and hypoglycemia point to adrenal involvement.

CLINICAL TYPES

One of the earliest types to be recognized is acromegaly. This type is too well known to need any detailed description. Closely associated with this type are the cases of gigantism. Both acromegaly and gigantism are due to hypersecretion of the anterior lobe; gigantism occurs in cases in which the epiphysial centers had not yet ossified, whereas, acromegaly usually occurs in adults; still cases of acromegaly have been reported in children by Antonini and Marzocchi, de Cyon, Rake, Salle and others. The most notable symptoms of acromegaly are skeletel overgrowth, main en large, phalangeal alteration, mandibular prognathism, spacing of teeth, rounding of shoulders, sterno-

clavicular enlargement, peculiar cranial configuration and hypertrichosis.

Type Fröhlich.—To this type belong those cases which have neighborhood symptoms of tumor of the hypophysis, without any evidences of acromegaly; these cases have a peculiar adiposity, with a feminine type of distribution of the fat when it occurs in males. There is aplasia of the genitals, hypotrichosis, subnormal temperature, undersized stature, psychoses of varying nature and increased carbohydrate tolerance. These cases are due to hyposecretion of the posterior lobe. Such cases in children have been reported by Frölich, Babinski, Hochwart, Uhlthoff, Cagnetto, Erdheim, Israel, Woolcombe, Creutzfeldt, Cushing and others.

Type Burnier.—In 1912 Burnier collected a group of cases from the literature and added one of his own cases, which, in addition to local signs of hypophysial tumor and signs of posterior lobe insufficiency, showed marked dwarfism. These cases are due to hyposecretion of both lobes. The most important symptoms of this type are optic nerve atrophy (almost invariably present), adiposity, dwarfism and atrophy of external and internal genitals. Such cases have been recorded by Burnier, Kon, Benda, Hutchinson, Heuter, Bartels, Nazair, Zöllner, Mixter and Quackenboss and others.

Type Cushing.—It is Cushing who pointed out that a pituitary may be hypersecreting at one time and hyposecreting at another, and that in fact all cases of hyperpituitarism show evidences of hypopituitarism as the disease progresses. It is he also who made the observation that one lobe may be hypersecreting and the other lobe hyposecreting at the same time; and thus we may have a variety of mixed types. He especially called attention to a case of skeletal overgrowth associated with adiposity and sexual infantilism without acromegaly.

DIAGNOSIS

Diagnosis of acromegaly and gigantism is simple; the Roentgen rays, however, are of great aid. They may show an enlarged sella turcica, or they may show enlargement, broadening and tufting of the phalanges. In posterior lobe insufficiency, the estimation of the sugar tolerance is of importance. We must always suspect posterior lobe insufficiency in individuals who can take more than 150 gm. glucose and 100 gm. levulose by mouth without glycosuria. In some cases of anterior lobe hyposecretion there is a thermic response when they receive an injection of anterior lobe extract. The symptom-complex of skeletal overgrowth or dwarfism, adiposity, genital atrophy, optic nerve atrophy, deformation of sella and increased carbohydrate tolerance are absolutely pathognomonic of dyspituitarism.

DISTURBANCES OF THE ADRENALS

The first definite account of the adrenals is given by Eustachius in 1563. In 1849 Addison observed that certain cases of disease, characterized by pigmentation of the skin, languor, and other symptoms, are associated with destruction, usually tuberculous, of the adrenal bodies. It was Trousseau who first called the condition Addison's disease. In 1894 Oliver and Schäfer discovered the blood pressure raising activity of extracts of the medullary portion of the gland. In 1901 Blum discovered that glycosuria is produced in certain animals following hypodermic injections of epinephrin. In 1897 Abel and Crawford isolated in crystalline form the active principle of the medulla of the gland. Epinephrin and iodothyroglobulin are the only definite internal secretions which have yet been isolated. The adrenal gland is built up of two entirely different tissues. Its medulla is composed of semifluid cells; these cells secrete epinephrin and when heavily loaded with this substance they take a yellow brown stain with chromate salts from which they have acquired the name of chromaffin cells. The cortex forms in man at least 90 per cent. of the entire bulk of the gland. In an encephalic fetus, the cortex is very deficient. The cortical cells seem to be concerned in supplying some secretion which influences the growth and reproductive powers of the animal; these cells are of greater vital importance than the medullary cells.

Diabetic puncture is ineffectual in animals from which the adrenals have been removed; further, in such animals the glycosuria resulting from the extirpation of the pancreas is much reduced. After prolonged use of epinephrin there is marked hypertrophy of the islets of Langerhans as well as of the adrenal bodies. As pointed out by Schäfer, there seem to be connecting links between the glycosuria set up by pancreatic removal and that due to the action of the epinephrin. After extirpation of the adrenals glycosuria cannot be produced by central puncture or by removal of pancreas. Zuelzer found that extirpation of the pancreas carried out at the same time as ligature of the adrenal veins provokes little or no glycosuria. Loewi reports that in diabetes arising after extirpation of the pancreas, epinephrin produces dilatation of the pupil if applied to the conjunctiva, whereas it has no influence on the normal eye. To summarize, it may be said that the function of the medullary portion is to sustain the cardiovascular tone and to produce an antitoxic substance capable of neutralizing toxic products of muscular activity and other undetermined poisons. There are three views as to the function of the cortex: Some believe that it has to do with the growth and development especially of the reproduc-

tive organs; others, that its main function is the neutralizing of toxic substances, and still others that it has to do with the internal secretion of the medulla. Falta believes that the cortex is a trophic center for beard growth and for the growth of hair on the body.

CLINICAL TYPES

Hypo-Adrenia

Addison's Disease.—The symptoms of this disease are too well known to need any detailed mention here. Reference to the physiologic action of epinephrin will explain many of the symptoms which occur in this disease as, hypothermia, coldness, asthenia, hypotension, emaciation, and tendency to syncope. Bronzing is due to an accumulation of melanin in the epidermal layers of the skin, and Sajous believes that the constituent of the oxidizing substance which becomes oxidized when melanin is formed is the adrenal secretion.

Functional Hypo-Adrenia.—Patients suffering from deficiency of adrenal secretion complain of asthenia and are very sensitive to cold; their extremities are always cold and they present the following symptoms: weak cardiac action, and pulse, anorexia, anemia, slow metabolism, constipation and psychasthenia. Children with deficient adrenal secretion are pale and emaciated; they have cold hands and feet and flabby muscles; their appetite is capricious and the blood pressure is low.

Hyperadrenia

Tumors of Cortex.—In hyperadrenia due to tumors of the cortex, there is an accelerated development of the body and a premature development of the genitals; the infantile type of skeleton, however, is preserved. In some cases there is adiposity; in girls there is premature onset of menstruation and development of the breasts; the hair on the mons veneris, in axilla and on the genitals develops early. Out of seventeen cases collected by Glynn fourteen were in girls. The especial feature of these cases is the early excessive development of the secondary sexual characters and the external genitals; many of these cases present adiposity; associated with the excessive and premature development of body and muscles there is premature ossification and dentition; the mental development of these patients usually corresponds with their age and not with their physical development; the sexual desires are overdeveloped but not to the same degree as are the genitals.

In older children, the symptoms of hypernephroma also manifest themselves by overdevelopment of the sexual sphere. In older girls, menstruation ceases, there is atrophy of the uterus, hypertrichosis of

masculine type (beard and mustache), hair begins to grow on the whole body, and universal adiposity develops.

It is of interest to note here that in many cases of pseudohermaphroditism of the feminine type, there is found a bilateral hypertrophy of the adrenal cortex.

The enlargement of the adrenal cortex, during breeding, during pregnancy, after castration, and the small size in deficient sexual development are additional evidence of the association of the cortex with sex characters.

DISTURBANCES OF THE THYROID AND THE PARATHYROID

In 1873 Sir William Gull gave the first account of myxedema under the name of "a cretinoid state supervening in adult life in women." Sporadic cretinism was described before this by Hilton Flagg. In 1877 Ord proposed the name myxedema. The symptoms which follow total thyroidectomy were described by J. L. Reverdin in 1882. In 1883 Kocher called this symptom complex "cachexia strumipriva." The foundations of our present method of treatment have been laid by Schiff, who had shown that successful transplantation of a thyroid gland in a dog sufficed to prevent the development of the symptoms which usually followed its removal. In 1890 Horsley suggested that grafting should be tried as a means of arresting the progress of myxedema. In 1891 Murray was first to suggest the internal administration of the gland (hypodermically); in 1892 MacKenzie and Fox showed that the extract was equally active when given by mouth.

The parathyroids were first described by Sandström in 1880. In 1891 Gley rediscovered them. The modern theory of the supreme importance of the parathyroids was first clearly put forward by Gley, and has since been elaborated by Vassale and Generali and others.

There are three directions in which the evidence of a functional relationship between the thyroid and the parathyroid glands may be regarded as conclusive:

1. There is the favorable influence of thyroid treatment in the tetania parathyreopriva of animals.

2. We have certain proof of hypertrophy of the external parathyroids, after extirpation of the thyroid gland.

3. There is hypertrophy of the thyroid which follows removal of parathyroids.

In India tetany is a disease of child-bearing women and there is a marked family tendency to the disease. The children of women who suffer from tetany are frequently cretinous. Idiopathic tetany was first described in 1830 by Stringheim.

CLINICAL TYPES

Hypothyroidism

There are three well-recognized types of hypothyroidism: myxedema adultorum, sporadic cretinism, and cretinoid degeneration, which includes simple goiter, goiter heart, endemic cretinism, and endemic deafmutism. The symptoms of these various types are too well known to need repetition here. Differentiation of endemic from sporadic cretinism may be of interest, as cases of the former type may be puzzling and misleading unless one thinks of them. The effect of thyroid therapy is not so constant as in sporadic cretinism; the real myxedematous symptoms are wanting in many cases or are very slight; the manifestations of endemic cretinism are far more manifold. It is these cases which develop deafmutism, and in them are often seen great discrepancies between the physical and mental symptoms. Many of the endemic cretins show little backwardness in their mental development, although they may have all the physical characteristics of cretins, and on the other hand, some may show cretinous idiocy with but little retardation in growth. In endemic cretins growth is only delayed; even in the most severe cases union of epiphyses takes place.

Although the clinical entities mentioned in the previous paragraph are well recognized, there are many patients who present symptoms of slight thyroid insufficiency, which we are daily overlooking because the symptoms are not so well recognized.

Symptoms of Uncomplicated Slight Thyroid Insufficiency

The most important symptoms are (1) transitory infiltrations of the skin; (2) hirsute derangements, as partial alopecia, capillary nanism, premature baldness and grayness, absence or premature falling out of the eyebrows; (3) caloric disturbances as coldness of extremities, chilliness, shivering fits, subnormal temperature, chilliness with vasomotor derangement, of which acro-asphyxia, cyanosis, and chilblains are the manifestations; (4) anorexia, tendency to obesity and constipation; (5) fatigue and somnolence; (6) small size of patients and retardation of certain developmental processes (dentition, walking, speech); (7) tendency to muscular and articular pains and frontal and occipital headaches, as well as to apathy, indolence and depression, and (8) imperfect development of sexual glands, and diminution of sexual appetite.

Simple inadequacy of the thyroid is rarely observed clinically but is almost invariably associated with symptoms of thyroid excess. The symptoms of slight hyperthyroidism are (1) hypertrichosis and hyperthermia; (2) acro-erythosis with cutaneous humidity; (3) emaciation and diarrhea; (4) restlessness, insomnia; (5) excessive height, developmental precocity, "syndrome of persistent juvenility"; (6) large,

brilliant protruding eyes with nystagmiform movements, extreme nervous irritability with cardiac and nervous excitability, and (7) hyperthyroidic syndromes, as migraine, ophthalmic migraine, asthma, chronic rheumatism, mucous enteritis, urticaria and certain mental symptoms.

Hyperthyroidism

In 1840 Basedow described three cases of the disease which now bears his name. In 1835 Graves described the same disease, which he believed to be related to hysteria. It was Möbius who in 1886 showed the relationship of Basedow's disease to hyperthyroidism.

Holmgren had shown that Basedow's disease in children leads to accelerated growth and premature union of the epiphyses. Schkarine reported a case of the disease in a 4½ year old girl who showed abnormally rapid growth. The skeleton of such patients is gracile, and the end phalanges are pointed. In males there is impotence and a loss of libido. In women amenorrhea is an early symptom. In cases in which the disease is of long duration there may be complete atrophy of the entire genital apparatus. Conception in morbus Basedowi is rather infrequent.

Of 3,477 cases only 184 occurred in children under 15. White Clifford reported a case in an infant: the mother had one previous infant with Basedow's disease. Often a number of members of the same family have it; Oesterreich reports ten cases in one family.

It is now possible to distinguish the symptoms of Graves' disease which might be due to irritation of the sympathetic from those which might be attributed to autonomic stimulation.

BASEDOW SYMPTOMS

Sympathetico-Tonic	Vagotonic
1. Pronounced protrusion of the bulb.	1. Relatively moderate degree of tachycardia.
2. Von Graefe absent.	2. Pronounced subjective heart symptoms.
3. Loewi's phenomenon positive.	3. Von Graefe definite.
4. Mobius positive.	4. Wide lid clefts.
5. Dry bulbs.	5. Möbius absent.
6. Greatly increased activity of heart with less pronounced subjective disturbances.	6. Slight protrusion of the bulb.
7. Sweating and diarrhea absent.	7. Increased lacrimation.
8. Falling out of hair.	8. Profuse sweating.
9. Eosinophilia absent.	9. Diarrhea.
10. Inclination to fever.	10. Disturbances of digestion.
11. Alimentary glycosuria.	11. Eosinophilia likely.
12. Refractory behavior to pilocarpin.	12. Alimentary glycosuria absent.
	13. No epinephrin glycosuria.
	14. Pigmentation.

In 1895 von Mikulicz called attention to the occurrence of enlarged thymus in severe cases of exophthalmic goiter. In 1899 Rehn sug-

gested that it might be well to attack the thymus gland surgically in this disease. Halstead says "that the thymus plays an important part in Graves' disease has, I think, been demonstrated beyond question by the results which have followed thyroidectomy. That some sort of relation exists between the two organs we have further evidence from the physical examination of the nonfatal cases, from the autopsy table and from experiments on animals." In 40 per cent. of exophthalmic goiter cases the thymus is persistent. Symptoms of Graves' disease which indicate a preponderant influence of the thymus are the vagotonic symptoms. The blood picture in Basedow's is also due to the thymus.

DISTURBANCES OF PARATHYROIDS

Tetany is the most marked example of insufficient secretion of the parathyroid glands. Tetany occurs in children; it may arise idiopathically in adults, in maternity cases, in certain stomach diseases, in certain infectious diseases and under other conditions. The symptoms of tetany are too well known to need any repetition; only those which have a bearing on other ductless glands will be mentioned here.

In thyroidectomized dogs the glycosuric action of adrenin is diminished; in parathyroidectomized dogs, however, it is increased; in such animals there is also a diminished tolerance for carbohydrates. The trophic disturbances in tetany affect only tissues of ectodermal origin, as hair, nails, skin, gums, and cilliary epithelium; in chronic tetany falling out of hair is common; the nails become brittle; the skin in acute cases assumes a pseudo-edematous appearance. Often pigmentation of skin is observed. Of great interest is the development of cataract in these cases. In chronic insufficiency of parathyroid secretion there is defective development of the teeth and the bones. Some believe that such deficiency in infants leads to rickets, and in adults to osteomalacia. Other diseases which have been attributed to deficient parathyroid secretion are paralysis agitans (Landberg, 1904, Berkley, 1905), myotonia, myoclonia and myoclonic epilepsy. The coincidence of epilepsy and tetany is not infrequent. Redlich collected reports of seventy-two such cases from the literature.

Hyperparathyroidism.—In the few cases of adenoma of the parathyroids reported no signs of hypersecretion were noted. Lundberg and Chvostek believe that hypersecretion of the parathyroids is responsible for myasthemia paralytica. Others believe that myatonia periodica is also due to the same cause.

DISTURBANCES OF THE PINEAL

There are only about fifty cases reported in the literature: they are mostly due to cysts, gummata or tumors. Pineal disturbances usually affect young individuals. They are usually due to developmental defects, and are far more frequent in the male sex.

Like the hypophysial tumors, they may give the general symptoms of brain tumors with certain focal signs, and in addition, by interfering with physiologic function, may bring about distinct and characteristic disturbances in nutrition. In enlargements of the pineal, circulatory disturbances develop first, with the formation of varying degrees of hydrocephalus.

The neurologic symptoms are those of increased cerebral pressure, due to the hydrocephalus; they are always present and are among the first noted. Headache is the first symptom and is mostly occipital. Other symptoms are papillary edema, abnormal drowsiness, increased muscular tonus, weakness without paralysis of the extremities and increased reflexes. Pressure on corpora quadrigemina gives rise to ocular and papillary signs, isolated eye palsies and nystagmus. Other symptoms are giddiness and dizziness, staggering gait, asynergia and adiadochokinesis; less constantly excessive thirst, polydipsia with polyuria; glycosuria was observed in a number of cases.

The metabolic symptoms are adiposis, early sexual maturity, and later cachexia. The trophic disturbances are of most interest. There is a rapid and abnormal development of the body and premature development of the genitals. In these cases there is enlargement of the penis, with increase in genital hair and in the general hairiness of the body, increased libido, early masturbation, and in some cases changes of the voice.

Marburg believes that hypopinealism leads to premature development of the genitals, hyperpinealism to general adiposity and epinealism to cachexia.

DISTURBANCES OF THE GONADS

In the gonads (testes-ovary) there are two kinds of tissue, the interstitial tissue and the specific genital gland. The interstitial cells of Leydig in man are of the greatest importance for the development of the primary and secondary characteristics. One of the functions of the male gland may be affected without the other; for instance in abdominal cryptorchism there is no development of secondary male characteristics, but there may be spermatogenesis. In the adult, inguinal cryptorchism leads to no loss of libido. Such men may have ejaculations without spermatozoa; they are potent but sterile. They have the virile habitus; there is beard growth, skeleton is normal. Here the interstitial cells have developed but the genital cells have not. Tandler found in twenty cases of cryptorchism, spermatogenesis not once, and normal interstitial tissue in all. Ancel and Bouin tied the vasa deferentia; after a considerable time spermatogenesis ceased, but the interstitial cells were not affected. Roentgen rays affect the genital cells but not the interstitial cells.

The female and male bodies resemble each other far more before puberty than later; before puberty they both show the infantile type. In man at time of puberty the larynx enlarges, the voice changes, beard growth becomes prominent; in woman the breasts develop, the pelvis assumes the more feminine type, the form becomes more rounded, there is a deposition of fat around the hips. In both sexes there is a growth of hair on mons veneris and axillae; in woman the hair line is horizontal, whereas in man it is triangular. In man the extremities are longer in proportion to the body length.

HYPOGONADISM

Eunuchism.—If castration is carried out early, the development of the secondary sexual apparatus remains very much undeveloped (penis, prostate and seminal vesicles remain very small). In older people the penis becomes only a little smaller but the prostate diminishes considerably. There are no erections and no libido; if castration is done late, libido may remain and the subject may have ejaculations of prostatic fluid. The character of such people is entirely changed; the intelligence remains normal. Growth is accelerated and the subject may reach a height of 200 cm.; the union of the epiphyses is delayed, also ossification of sutures of head. The head is small, and the back of the head is flattened; the neck is short; the extremities are long and lower part from umbilicus is longer than above. The pelvis remains infantile; the voice and the larynx remain childish. The bones remain delicate and the muscular markings are fine; the skin is thin and pale and of yellow discoloration. There is adiposity of feminine type, a horizontal fold of fat at the mons veneris, and a deposit of fat on the nates, on the hips, thighs, mammae. The secondary male characteristics are poorly developed. The hair on the head is well developed, no beard growth, no hair on body, in axilla, or on scrotum and perineum.

Castration after puberty in women leads regularly to atrophy of the uterus and vagina; menstruation ceases, the clitoris shrinks and libido diminishes; in a few cases there was increased libido for a time; adiposity generally present.

Eunuchoidism in Adults.—Here we get all the symptoms of eunuchs except the bone changes, as the epiphyses have already united. The penis, testicles, and prostate all become small and atrophy; there is no libido; impotence is present; there is a retrogression of all the male secondary sexual characteristics. In women there is a retrogression of the genitals and adiposity and a loss of pigment, but no loss of hair in axilla or from mons.

HYPERGONADISM

Hypergonadism has been noted in children suffering from malignant disease of ovary or testicle. In these cases there is enormous development of the body; the hair on the mons, in the axilla, and on the face begins to grow; hair grows also over the whole body. Libido is developed as in adults. Intelligence is well developed but childish; premature change of voice takes place. Erections and ejaculations have been noted as early as in the first year; in these cases the hyperdevelopment of the genitals precedes the development of the body. There is premature closure of the epiphyses, so that these children are too big for their age, but they cannot become giants; the body shows infantile dimensions.

In females, there is menstruatio praecox; the uterus, vulva and breasts are overdeveloped. There is excessive bodily growth; dentition, changes of teeth, ossification of bone centers, and closure of epiphyses are premature. One of these children was impregnated at 8 years; shortly after this the abnormal growth ceased; she died at the age of 75 years (von Haller).

DISTURBANCES OF THE THYMUS

Neusser reported a case of tumor of the thymus in a man aged 25 years; the patient was very tall and hypoplasia of the genitals was present. In many cases of myasthenia gravis, hyperplasia of the thymus is found. After operative removal of the gland, even in infancy, hardly any symptoms are observed. But in most of these cases only partial removal was performed so that no definite conclusions can be drawn. Thymus hyperplasia is very often found in Basedow's disease, in acromegaly and in eunuchs.

Katz, in each of sixty-one mentally normal children who died of various diseases, found a normal thymus; in each of twenty-eight mentally feeble children, the thymus was absent. In another series of 292 cases of mentally deficient children the organ was absent in 74 per cent. Lange, Decker, Garri, and Lampè have reported cases of idiocy in which at necropsy the thyroid was found quite normal; the thymus was very small.

Ruhräh and Thompson found atrophy of the thymus in marasmus cases. Thymectomy causes a gradual decrease in the leukocyte count, while an administration of thymus causes an increase of these cells.

In status thymolymphaticus, there may be increased height, gigantism, or dwarfism; the bones may present deformities as in osteitis deformans or acromegaly. The head may be larger or smaller than normal and may present other anomalies; the extremities are long; the epiphyses close late. The facies is pasty and anemic. Adiposity of a

eunuch type is usually present; the development of male secondary characteristics is deficient; the male form approximates the female configuration. Hair supply is deficient on body, and scrotum; no beard growth; voice is high pitched; pomumadami only slightly developed; penis, testicles and prostate all small; cryptorchism and aspermatogenesis are often present. This description given by Neusser corresponds very clearly with our present conception of hypogonadism; and as in most of Neusser's cases there was concomitant cryptorchism and aspermatogenesis it is very likely that the symptom complex which he ascribes to status thymolymphaticus may be due to hypogonadism.

In women Neusser noted a deficient hair growth; menstruation delayed or entirely absent; uterus hypoplastic; pelvis small; infantilism of internal genital organs; manly voice; masculine build of larynx and distribution of hair; flat breasts, small hips, hypoplastic heart; congenital mitral stenosis and other congenital heart anomalies, especially congenital narrowing of the aorta and other blood vessels.

DISTURBANCES OF THE PANCREAS

Bouchardt observed sclerotic changes in the pancreas in cases of diabetes. Mering and Minkowski proved that total extirpation of the pancreas in dogs leads to glycosuria. The opinion was expressed by Laguesse (1893) that the so-called islets of Langerhans may be the seat of the internal secretion of the pancreas. Opie and Weichselbaum proved that in diabetes mellitus the islets are the seat of pathologic lesions.

In the glycosuric stage of diabetes, injections of epinephrin increase the output of sugar, but in the aglycosuric stage no such increase is noted. After thyroidectomy, however, epinephrin glycosuria is diminished, but after parathyroidectomy it is increased.

Claude Bernard could produce glycosuria by puncturing a spot in the fourth ventricle. This glycosuria is produced through the sympathetic system; if the spinal cord above the outlet of the sympathetic is broken no such glycosuria results. Electric stimulation of the splanchnic produces glycosuria. Glycosuria is also found in cerebral hemorrhages, encephalomalacia, tumors of the brain, and especially in tumors of the fourth ventricle.

Hyperglycemia is also produced in extirpation of pancreas, in Bernard's puncture, or puncture of the medulla, stimulation of the splanchnics, and by the introduction of an excess of epinephrin into the blood. An increased sugar tolerance is observed in hypothyroidism, in hypopituitarism and in hypo-adrenalism. In hypogonadism, although there is adiposity, the tolerance for carbohydrates is limited and alimentary glycosuria is more easily evoked.

In many cases of diabetes there is increased excitability of certain sympathetic nerves, especially of the dilator of the pupil, of the liver, kidney and other organs; but the excitability of the autonomic nerves is not diminished.

In diabetes, impotence is usually found in men, but there is no recession of the secondary sex characteristics. Often there is atrophy of the testicles. In women menstruation is not disturbed but conception is rare. Bramwell and Reutone have described cases of pancreatic infantilism in children.

CLINICAL MANIFESTATIONS OF PLURIGLANDULAR DISTURBANCES

To the axiom that a man is as old as his arteries may be added that a child is as old as its ductless glands. The ductless glands, like other organs, may prematurely degenerate; at times this is due to inherited insufficiency of the glands, to infection, or to intoxications; the result is a sclerotic atrophy of a number of these glands. Most affected are the thyroid gonads, hypophysis and adrenals. In addition to symptoms of deficient secretion of these glands a terminal cachexia usually develops.

All these cases show symptoms of late hypogonadism. Cachexia and anemia are prominent symptoms; no adiposity occurs, but emaciation with weakness is nearly always present. The face and other parts of body are swollen as in myxedema. Alopecia and loss of hair on the whole body usually take place; pigmentation of skin and mucous membranes is a prominent symptom. Anemia and transient polyuria are at times present. In women degeneration and atrophy of the genital apparatus and of the secondary sexual characteristics is very marked.

In these cases, degeneration of the genitals and retrogression of secondary characteristics is referable to hypogonadism. Alopecia, trophic disturbances of the nails, and teeth, the apathy, headaches and amnesia and myxedematous skin are due to hypothyroidism. The cachexia and the transient polyuria suggest the involvement of the hypophysis. The hypotonia, the severe asthenia and the pigmentation point to the involvement of the adrenals. Spasmophilia and tetanic contractions suggest that the parathyroids may also be involved.

Thompson in a case of marasmus found marked sclerosis of all the ductless glands. Hutchinson, Gilford and Variot and Pironeau* have reported cases of pluriglandular involvement in children. Variot named these cases *nanisme type sénile*. The cases reported by these

* Since the article was written another case of progeria was reported by C. W. Rand, Boston Med. and Surg. Jour., 1914.

writers resemble each other as do all cases of cretinism. There is retardation of growth in these cases (may be dwarfed); emaciation with folding of the skin is a prominent symptom. The muscular development is good, but the skeleton remains infantile; the bones are delicate, ends are thickened and the epiphyses close prematurely. The genital development is much retarded; there is deficient hair growth over the whole body, including head and eyebrows, which imparts to these patients a very senile appearance. On necropsy in one of these cases only sclerosis of the pituitary was found. Intelligence in these cases was good. Gilford has named this condition "progeria."

"INTERRELATION OF THE DUCTLESS GLANDS"

Although our knowledge of the internal secretions is incomplete and confused, much progress has been made in this branch of medical science in the last decade. One fact has been clearly brought out and that is that the physiologic relation of all ductless glands is an intimate one, and that in pathologic conditions of one of them all the other glands are affected. The influence of one gland on another may be compensatory or inhibitory.

The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the possible interrelations of endosecretory organs. The pituitary hypertrophies as a reaction of hypothyroidism. The thyroid exercises normally an inhibition on the pituitary, but stimulates the adrenals; the adrenals inhibit the pancreas, and the pancreas inhibits both the thyroid and the adrenals; the adrenals, however, stimulate the thyroids. In Basedow's disease we have menstrual disorders, amenorrhea, and often atrophy of sex organs; in myxedema we have sex depression, impotence and atrophy of the genitalia. There exists some relationship between these organs, and it is probable that the thyroids have on the sex organs a stimulating effect that is necessary for the normal continuance of their function. In Basedow's disease and in simple congenital goiter, the thymus is often enlarged. In Switzerland the offspring of goitrous mothers often have both thymus and thyroids enlarged. Thyroidectomy raises the assimilation limit for dextrose; therefore the thyroid inhibits the pancreas in its function of promoting glycolysis.

The pituitary has a slightly stimulating effect on the thyroid. These glands are more or less synergic and either can to some extent function vicariously for the other. Cushing found atrophy of the gonads after extirpation of part of the anterior lobe. In acromegaly there is cessation of menstruation, impotence in the male, and atrophy of aplasia of the genitals. The pituitary, therefore, supplies a secre-

tion that stimulates the sex glands to activity. After prolonged feeding of pituitary there is hyperplasia of the adrenal cortex.

A theory that the adrenals are related to the sex functions was proposed by Meckel as early as 1906. It was based on the following grounds: 1. In certain aborted fetuses he had noticed that both the adrenals and the gonads were lacking. 2. In animals in which sexuality is marked the adrenals are notably large. 3. In birds and amphibia the gonads and the adrenals are closely associated in position. 4. He had

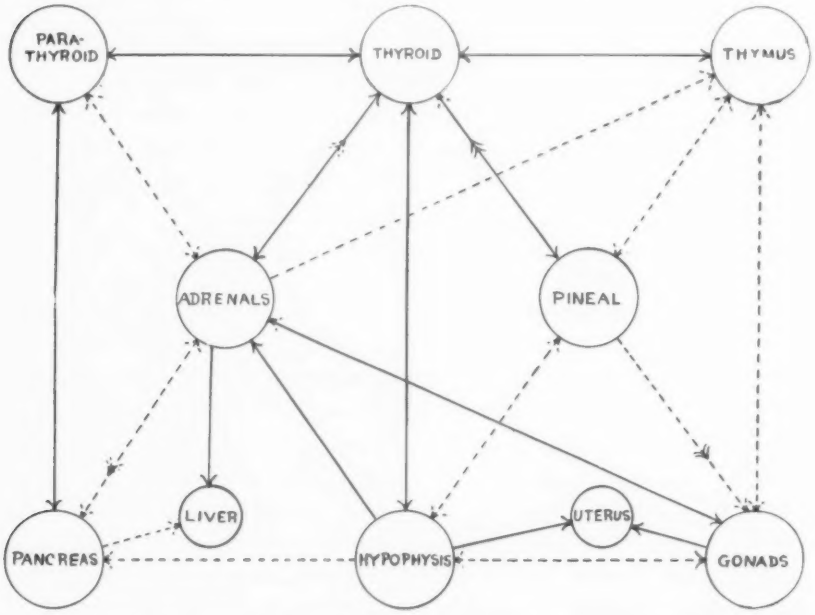


Fig. 1.—Chart showing interrelation of endocrine organs. ⟶ stimulates; - - - ⟶ inhibits; ⟷ cooperate; ⟷ - - - ⟷ antagonize; A ⟷ « ⟷ B - - - » - - - ⟶ C; A and C cooperate « »; A stimulates B⟶; B inhibits A ⟵; B inhibits C - - - ⟶; C has no action on A.

noted adrenal degeneration in several cases of disease of the genitalia. In cases of hermaphroditism marked hypertrophy of the adrenals is sometimes observed. The clinical literature indicates that there is a correlation between the adrenals and the gonads. It further suggests that the adrenals furnish a stimulus to the gonads. In Addison's disease there is hypertrophy of the thymus. The adrenals and the pancreas are mutually antagonistic. In Addison's disease the dextrose limit is high.

Castration causes hypertrophy of the anterior lobe of the pituitary; pregnancy also causes increased activity of the hypophysis. The pituitary is normally held in check by the gonads and when this inhibi-

tion is removed the pituitary manifests increased activity. The gonads exert a depressing effect on the thymus; the adrenal cortex hypertrophies after castration: the thyroid hypertrophies in menstruation and in pregnancy (Fig. 1).

INFANTILISM

The term "infantilism," devised by Laségue, means the maintenance of the genital organs in the infantile state of development, with a lack of secondary sex characteristics; there is a failure of the primary and the secondary sex characteristics to appear at the proper time. This may occur in individuals of dwarf growth, of normal growth, and in giants.

Infantilism occurs: (1) in the dwarfing of growth from intoxications as chronic tuberculosis, congenital lues, malaria cachexia, leprosy, pellagra, in severe rickets, chronic alcoholism in childhood, after prolonged and excessive doses of mercury, lead, morphin, tobacco and carbon bisulphid; (2) in all abnormalities of growth which seem to depend on the gross lesions or defects of important internal organs as thyroid, pituitary, gonads, thymus, pancreas, adrenals, kidney, and liver (in fact all dwarfs except achondroplasiacs present infantilism and puerile habitus); (3) in disturbances of growth associated with disturbances of the circulatory system either congenital or beginning very early in life, congenital stenosis of the aorta, stenosis of mitral and aortic valves of the heart, and general defects of the circulatory system; (4) in conditions such as congenital adiposis, progressive muscular dystrophies, microcephaly, spastic diplegia, and ateliosis.

The Brissaud type of infantilism manifests itself mainly by the persistence of the characteristics of childhood, physical and mental, without the evidences of true idiocy and often without true dwarfism. This type of infantilism is probably due to hypothyroidism, and presents the symptoms of myxedema in a mild form.

"DWARFISM"

Dwarf races seem to have been mentioned in the literature and legends of most languages. Schweinfurth found at the court of King Munza representatives of a dwarfed race to whom he applied the name "Akka." There is among the proletariat of European cities and elsewhere, a great group of very undersized individuals; these are said to be especially common in Bavaria and Italy. Among famous dwarfs may be mentioned Æsop, Philetas of Cos, Alypius, Licinius Calvus, Characus, and Carrie Akers, height 2 feet 10 inches, weight 309 pounds.

Growth depends on inherited disposition, nutrition, conditions of life, as surroundings or environment, and habits of life; pathologic

influences may affect any of these. Dwarfs may be classified into (1) cases which may be possibly caused by either changes of condition or by inherited tendency or both; (2) cases occurring in one or more children, as the defective growth which occurs in lues, in children of drunkards, or those affected by plumbism or other poisons; and also cases of ateliosis or true dwarfism; (3) cases in which influences to growth are brought to bear during intra-uterine life, for instance, dwarf growth of microcephaly or porencephaly; (4) cases in which adverse influences have been exerted during childhood; here, development, at first normal, has after an illness ceased to advance at the usual rate, for instance, in acquired hydrocephalus, chronic meningitis, malaria, cachexia, granular kidney, pneumonitis, congenital heart disease, early acquired heart disease, chronic alcoholism in early childhood; (5) cases due to disorders of the pituitary, thyroid, thymus, adrenals, pancreas and intestine (Herter); (6) cases occurring in connection with rickets, ateliosis, and achondroplasia.

Dwarf growth may be the result of insufficient development, the premature ossification, and the early union of the epiphyses and diaphysis (achondroplasia). Or it may be due as in true dwarfs (ateliosis) to a persistence of the cartilage disks throughout life. In these cases epiphyses do not join the diaphyses; in many bones the epiphyses do not appear at all, being represented by cartilage as in the infant; there is no disproportion in the trunk and the extremities. In cretins the cartilage of conjugation persists, ununited with the diaphysis. Eruption of teeth is disturbed in all dwarfs except achondroplasiacs; persistence of milk dentition and delayed eruption of last molars, are common in true dwarfs, in cretins and in microcephalics.

Achondroplasiacs enter the world as such; in true dwarfs the stunting of growth may be congenital or acquired soon after birth or during infancy, or childhood; in these, growth may be retarded to a minimum, or it may be very slowly continuous until quite late in life (thirtieth year). In others growth, having ceased, may recur and slowly continue until still later in life. Few of these reach old age, but many have lived 100, 90, 80, or 75 years.

Ateliosis resembles cretinism in facial appearance and in the same peculiar configuration of the skull. Defective development of the genital organs and the puerile habitus are other features common to both. In the true dwarf the deficiency of intelligence occasionally goes as far as idiocy. These two groups seem to merge into one another. And if ateliosis is to be considered a manifestation of dysthyroidism, then achondroplasia must also so be considered, for these two conditions present diametrically opposed symptoms. Myxedema in association with achondroplasia has been recorded more than

once; sporadic cretinism and achondroplasia may occur in different children of the same family. Dr. Hergothe has also alluded to the existence in the same family of achondroplasia and obesity, rickets and myxedema. Cavazanni records a case of achondroplasia in a child whose mother was afflicted with Graves' disease, and Duranti one of similar association, in which the mother died of liver and renal disease.

The differential points between ateliosis and achondroplasia will be noted from the following:

ACHONDROPLASIA

Height: Smallness of height, 3 feet 6 inches; 4 feet, 3 feet 2 inches.

Head: Large, round, brachycephalic; frontal and parietal eminences prominent; face small but with large features.

Muscular Development: Excessive; arms are muscular, very short; tips do not touch beyond the great trochanters.

Limbs: The lower limbs are short and massive; show angular deformities above and below the knees. Midpoint may be a quarter of the total height above the symphysis; shortening of limbs is of rhizomelic type. Hands and feet are short, thick, broad fingers of equal length. Main *en trident.*

Nose: Is flat and broad, retroussé nostrils are large.

Genitals, intelligence, hair, trunk, larynx, skin, dentition normal.

ATELIOSIS

Height: At 9 years, 19⅓ inches; at adult age 32½ inches.

Head: Face and general appearance those of infancy; face is short and broad; head proportionally large, is high, quadrate, prominent eminences; lower jaw and chin are small; head is bracycephalic.

Muscular Development: The musculature proportionate to size; is weak and shows lineaments of childhood.

Limbs: Hands, feet and nails have shape and appearance of childhood; no deformation; the skeleton shows the ridges, grooves and points of musculative origin and insertion; are feebly marked; physical strength is small, though greater than that of children of the same height.

Nose: Bridge depressed; broad; saddle shaped; is short and undeveloped.

Genitals: Secondary sex characteristics wanting; are usually sterile; incomplete descent of testes is usual. There is usually but not always sexual infantilism.

Intelligence: Usually normal; may vary from slightly defective to idiocy.

Hair: No hair on face; neck is short and thick; on the head not abnormal.

Trunk: General bodily proportions are those of normal child; mid part a little above the upper border of symphysis; the proportionate length of the segments of the limbs to one another is also normal.

Larynx: Is small and undeveloped; voice high pitched.

Skin: Not thickened, though it shows wrinkling and bronzing.

Dentition: Delayed.

The Lorain type or dwarfism was described by Lorain (1820). The dwarfism is symmetrical; it nearly always affects males. There are no myxedematous symptoms present, and the genitalia are usually normal; the pubic and axillary hair is wanting. The stature is diminished and slender; the facial appearance, expression, and intelligence are normal. This is not due to hypothyroidism but to anangioplasia,

that is, a defective development of the arterial system, and to premature ossification. This condition is probably due to an underlying status lymphaticus.

GIGANTISM

Bollinger includes under giants only those who have attained a height of 205 cm. Brissand and Meige believe that acromegaly and gigantism are one and the same disease; that acromegaly is gigantism in a person in whom the epiphysis had not yet united. Sternberg found that 40 per cent. of all giants have manifestations of acromegaly, and that 20 per cent. of all acromegalics are giants. Gigantism is not infrequently met with in eunuchs and in cases of hypogonadism. Huchard and Launois reported a case in a son of a giant; this boy was of gigantic stature at 12 years; at 18 he was 197 cm.; the genitals were normally developed; he lived to 60 years and then developed typical acromegalic manifestations. In the early stages of acromegaly, there is increased sexual potency and libido at times, but usually there is impotence, whereas "the interstitial cells of Leydig" are not affected; or there is hyperfunction of these cells; but in giants without acromegalic symptoms, there are manifestations of deficient secretion of the Leydig cells from the beginning.

ADIPOSITY

Von Noorden divides adiposity into two classes; one depends on exogenous and the other on endogenous factors. Exogenous adiposity is due to overeating, which often leads to diabetes; the endogenous adiposity is due to disease of ductless glands. Von Noorden showed that glycogen fixation and sugar production may be disturbed, while the fat formation from carbohydrates, may still continue. The fat tissue absorbs the overproduced carbohydrates as fat; there is thus an actual diabetic metabolism disturbance, but without glycosuria; thus we may have a pancreatic adiposity.

Hypothyroidism leads to adiposity; hunger cures in these cases lead to weak heart, but thyroid administration causes great reduction of fat; other signs of hypothyroidism are present. There is much increased tolerance for carbohydrates.

In dystrophia adiposo-genitalis, the fat is distributed in a peculiar way. This really is not an adiposity, for if these patients become emaciated they still preserve the fat pads in their choice places. But at times there is general adiposity in hypophysial cases and then it is due to increased sugar tolerance. These cases do not respond to thyroid, but often do respond to pituitary or testicular extract. The adiposity of pineal disease is probably due to hypophysial involvement.

In adipositas dolorosa, there is a peculiar distribution of the fat; the fat masses are painful, later asthenia and psychical symptoms

develop. Dercum believes it to be a type of dysthyroidism. In eleven cases which came to necropsy, nine showed changes in the thyroid. Of seven cases in which the hypophysis was examined, five showed pathologic changes.

THE BLOOD

In all diseases of the thyroid, hypophysis, and adrenals there is a diminution of neutrophils and an increase of the mononuclears, especially the lymphocytes; in half the cases there is leukopenia and in many cases there is eosinophilia. One often finds the same blood picture in status thymolymphaticus, and it is possible that the blood picture in dysendocrinism may be due to an underlying condition of status lymphaticus.

SUMMARY

In hypogonadism in children, there is increased height; the skeleton is gracile and shows characteristic dimensions (from sole to umbilicus longer than above, wide span and small head). There is characteristic fat deposition and deficient development of secondary sex characteristics. The closure of epiphyses is delayed, as is the ossification of bone centers.

In hypothyroidism there is dwarfism or retardation of growth; the skeleton retains the infantile type; the closure of the epiphyses is much delayed; ossification of bone centers is retarded and the fontanels close late. The ossified bones show slight sclerosis; the bones are plump (in young people with Basedow's disease, there is slight acceleration of growth and premature closure of union). There is retardation of genital development but not to the same extent as in hypogonadism.

Hypopituitarism in children leads to retarded growth; closure of epiphyses and ossification of bone centers is delayed. There is hypoplasia of the genitals, and especially marked non-development of secondary sex characteristics; adiposity of hypogonadism type and skeletal dimensions also resemble those seen in hypogonadism. In young acromegalics, there is premature closure of epiphyses, marked accentuation of secondary characteristics, and premature thickening of the bones with exostoses. In other cases there is retarded development of the genitals with gigantism of type seen in hypogonadism.

In hypergonadism, hyperadrenalism and hyperpinealism, there is premature development of the whole body, accelerated growth with preservation of infantile dimensions, premature development of the genitals, and later, premature closure of the epiphyses; these children are too big for their age, but they can never become giants on account of the closure of the epiphyses.

The closure of the epiphyses and therefore the extent of growth seem to be under the influence of the gonads. The development of

centers of ossification and the length of the bones seem to be greatly influenced by the thyroid and the hypophysis. In growth retardation due to the thyroid the bones are plump, in that due to the hypophysis they are delicate. In children, however, in Basedow's disease the bones are delicate, and in young acromegalics, they are plump with exostoses.

The anterior lobe of the pituitary and the thyroid control growth; hypersecretion leads to increased growth or gigantism, diminished secretion to diminished growth or dwarfism. Hyposecretion of thymus and pancreas may also lead to diminished growth.

Hyposecretion of the posterior lobe of the pituitary causes adiposity; hypersecretion causes glycosuria and polyuria.

The secondary male sexual characteristics are controlled by the interstitial cells of Leydig and are greatly influenced by the adrenals. The adrenals seem particularly to be related to the growth of a hair on the face and body.

The genital organs are controlled by the interstitial cells, but are secondarily affected by the pituitary, the thyroid, the adrenals, the pineal and the thymus.

Adiposity is present in hyposecretion of posterior lobe of the pituitary, in hypopinealism, in hypogonadism, and in hypothyroidism. It is usually associated with increased tolerance for carbohydrates, except in hypogonadism, in which there is no such increased tolerance. Tendency to glycosuria is present in hypersecretion of posterior lobe of pituitary, in hyperthyroidism, and in hyperadrenalism. Hypothermia is usually associated with adiposity, and hyperthermia with cases in which there is a tendency to glycosuria.

Carbohydrate metabolism is primarily regulated by the pancreas and the adrenals; the pancreas regulates glycogen formation, and the adrenals glycogen fixation; protein metabolism seems to be controlled by the thyroid; the purin bodies by the hypophysis, and the thyroid and calcium excretion seems to be controlled by the parathyroids and the thymus. The hypophysis, the thyroid, and the parathyroids also influence carbohydrate metabolism by their secondary influence on the adrenals and the pancreas. For analysis of the other symptoms see chart.

*ILLUSTRATIVE CASES**

CASE 1.†—Hypopituitarism of both lobes with Basedow's disease (Fig. 2). A. K., 12 years of age. The patient had been complaining of headache, double vision, vertigo and vomiting; he was always cold and suffered a good deal from constipation. Weight 93 pounds, height 53 inches (12 pounds overweight, 4

* Cases 2 to 8, inclusive, are from the Pediatric Department of Vanderbilt Clinic, service of Dr. C. H. Smith.

† Case 1 has been previously reported in connection with an article on Dyspituitarism, AM. JOUR. DIS. CHILD., September, 1913.

TABLE OF VARIOUS CONDITIONS DUE TO DISTURBANCE OF DUCTLESS GLANDS

	Dwarfism	Skeletal Overgrowth	Skeletal Undergrowth	Premature Union of Epiphyses and Ossification	Delayed Union of Epiphyses and Ossification	Genital Hyperplasia	Genital Hypoplasia	Sexual Precociousness	Impotence	Adiposity	Increased Carbohydrate Tolerance	Glycosuria	Hypertrichosis	Hypotrichosis	Mental Precocity	Mental Dulness	Hypothermia	Hyperthermia	High Blood Pressure	Low Blood Pressure	Pigmentation	Asthenia	Cerebral Symptoms	Sellar Deformation	Tachycardia	Tremor	Spasmophilia	Polyuria
Pituitary:																												
Hypersecretion of ant. lobe types, Marie and Launois	..	+	..	..	+	..	+	..	+	..	..	+	+	..	..	..	..	+	..	+	+	+	+	+	..	..	..	..
Hyposecretion of post. lobe type, Frölich	..	..	+	..	+	..	+	..	+	+	+	..	..	+	..	..	+	..	..	+	+	..	+	+	..	..	..	..
Hyposecretion of ant. and post. lobes type, Burnier	+	..	..	..	+	..	+	..	+	+	+	..	..	+	..	..	+	..	..	+	+	..	+	+	..	..	..	..
Hyper of post. and hypo of ant. lobe, diabetes insipidus	..	..	+	..	+	..	+	..	+	..	..	+	..	..	..	..	..	+	..	..	..	..	+	+	..	..	..	+
Thyroid:																												
Hypersecretion — Basedow's disease	..	+	..	+	..	..	+	..	+	+	+	+	..	+	..	..	+	+	..	+	+	..	..	..	+	+	..	+
Hyposecretion — Cretinism	+	..	+	..	+	..	+	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Parathyroids:																												
Chronic hyposecretion, latent tetany	..	..	+	..	+	..	..	..	..	..	..	+	..	+	..	..	..	+	..	+	+	..	..	..	..	..	+	..
Adrenals:																												
Hypersecretion	..	+	+	+	..	+	..	..	..	+	..	+	+	..	..	+	..	+	+	..	+	..	..	..	..	..	..	..
Hyposecretion — Addison's disease	..	..	..	..	..	..	+	..	+	..	+	..	..	..	..	+	+	..	..	+	+	+	..	..	..	..	..	..
Gonads:																												
Hypogonadism — Eunuchoidism	..	+	..	..	+	..	+	..	+	+	..	..	..	+	..	..	+	..	..	+	+	..	..	..	..	..	..	..
Hypergonadism — Tumors	..	+	..	+	..	+	..	+	..	+	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Precocious maturity — Functional	..	+	+	+	..	+	..	+	..	+	..	..	+	..	..	..	..	..	..	..	..	..	..	..	?	..	..	..	..
Thymus:																												
Hypothymism — Status thymolymphaticus	+	..	+	..	+	..	+	..	..	+	..	..	..	+	..	+	..	..	..	..	..	..	..	..	..	..	..	..
Pineal:																												
Hyposecretion	..	+	+	+	..	+	..	+	..	+	+	..	+	..	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..
Pancreas:																												
Hypopancreatism — Diabetes mellitus	+	..	+	..	..	..	+	..	+	..	..	+	..	+	..	..	..	+	+	..	+	+	..	..	..	..	..	..	+
Pluriglandular Disease:																												
Hyposecretion, gonads, para and thyroid hypoadrenals	+	..	+	..	+	..	+	..	+	+	+	..	..	+	..	..	+	..	..	+	+	+	..	..	..	..	+	+	+

inches under height). Facies was peculiar and expression anxious; slight exophthalmos was present. Adiposity was of a feminine type of distribution; the genitals were hypoplastic and there was no axillary and no pubic hair. The pulse was 84 to the minute; the temperature subnormal. Bitemporal hemianopsia was present; mentality normal. The sella was enlarged and the centers of ossification were normal; the carbohydrate tolerance was increased to 250 gm. The presence of genital hypoplasia, hypotrichosis, adiposis, skeletal under-

Fig. 2

Fig. 3

Fig. 2.—Boy of 12, showing hypopituitarism of both lobes with Basedow's disease (Case 1).

Fig. 3.—Boy of 12 with functional hyposecretion of anterior and posterior lobes of the pituitary (Case 2).

growth with symptoms of cerebral pressure and enlarged sella suggest a tumor of the hypophysis; the presence of exophthalmos tachycardia and tremor suggests the presence of hyperthyroidism which is probably of a compensatory nature.

CASE 2.—Functional hyposecretion of anterior and posterior lobes of the pituitary (Fig. 3). F. P., aged 12, was brought for the rapid development of adiposity, which is of a feminine type of distribution. The temperature is subnormal. He complained of drowsiness and headache. Eye fundi were normal. Height is 4 feet 7½ inches; weight 111 pounds. The sella showed slight enlargement; the ossification centers were normal; the carbohydrate tolerance was increased. The adiposity, the hypoplasia of the genitals, the hypotrichosis, the hypothermia and the increased carbohydrate tolerance suggest posterior lobe insufficiency. Absence of cerebral symptoms rules out neoplasm.

Fig. 4

Fig. 5

Fig. 4.—Boy of 5 with hyposecretion of anterior lobe and hypersecretion of posterior lobe of the pituitary; diabetes insipidus (Case 3).

Fig. 5.—Child of 17 months with hypopinealism (Case 4).

CASE 3.—Hyposecretion of anterior lobe and hypersecretion of posterior lobe of the pituitary; diabetes insipidus (Fig. 4). O. F., aged 5 years. The patient had been passing a large quantity of urine (120-140 ounces per day) for the last two years; the thirst was very marked. Weight was 32 pounds, height 37 inches; temperature always about 100 F. Genitals were hypoplastic and the testes undescended. The urine showed a specific gravity of 1.007, no albumin, and had a trace of sugar. Roentgen ray of sella showed a very small pituitary; ossification of wrist centers was delayed; the hands were like those of a cretin. The mentality was normal. The polyuria and the glycosuria suggest hypersecre-

Fig. 6

Fig. 7

Fig. 8

Fig. 9

Fig. 6.—Child, aged 28 months, with hypothyroidism (Case 5).
Fig. 7.—J. A., achondroplasiac, aged 6 years.
Fig. 8.—A. A., aged 12. Precocious maturity.
Fig. 9.—Case of ateliosis, aged 23. Height 25 inches; weight 12 pounds.

tion of the posterior lobe; the skeletal undergrowth may possibly be due to hyposecretion of the anterior lobe.

CASE 4.—Hypopinealism. A. B., aged 17 months (Fig. 5). This case presents the following symptoms; adiposity, abnormal development of the breasts, and premature ossification of the head and bone centers of the wrists; circumference of the head only 17 inches; mentality far above that of usual infant of its age; marked spasticity of the legs and exaggerated reflexes. The fundi and the sella are normal. The precocious mental development, the adiposity, the premature ossification and the presence of cerebral symptoms with a normal sella suggest the presence of hypopinealism.

CASE 5.—Hypothyroidism (Fig. 6). I. S., aged 28 months; typical facies and hands of mild cretinism; marked physical and mental backwardness; genitals hypoplastic; temperature subnormal; ossification of bone centers of wrist much delayed; marked improvement under thyroid treatment.

CASE 6.—Achondroplasia (Fig. 7). J. A., aged 6 years.

	November, 1911	November, 1912	November, 1914
Head	20 inches	20 inches	20½ inches
Chest	18 inches	19½ inches	20 inches
Abdomen	20 inches	23 inches	20 inches
Length	29 inches	31½ inches	34½ inches
Weight	26 pounds	28 pounds	34 pounds
Navel-sole ...	13¾ inches	14½ inches	18 inches

CASE 7.—Precocious maturity? Hyperadrenalism? A. A., aged 12 years (Fig. 8), sister of child whose case is reported above. Began to menstruate at 10 years; she had been sent to a sanatorium for pulmonary tuberculosis. She shows abnormal development of the breasts and of the pubic and axillary hair. This is a case of precocious maturity or it may be a case of hyperadrenalism due to tuberculous involvement of the adrenals. The mentality was normal for the age.

CASE 8.—Ateliosis (Fig. 9).—The female (Fig. 9) is 23 years of age and is 25 inches in height; the weight is 12 pounds. Mentality is normal for the age. She presents no deformities; she is a true dwarf.

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